Answer 1:

Bibliographic Information

Effection of celecoxib combined with 5-Fu on treatment of human colorectal cancer in BALB/C nude mice subcutaneous xenograft model. Zhang, De-qing; Chen, Wei-chang; Wang, Lei; Chen, Gui-lin; Xie, Xue-shun. Department of Digestion Internal Medicine, The First Affiliated Hospital, SuZhou Medical University, Su Zhou, Peop. Rep. China. Zhongliu Fangzhi Yanjiu (2008), 35(6), 394-398. Publisher: Zhongliu Fangzhi Yanjiu Zazhishe, CODEN: ZFYHAB ISSN: 1000-8578. Journal written in Chinese. AN 2008:943752 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Objective To investigate the anti-tumor effect and explore its mechanisms of celecoxib (a selective cox-2 inhibitor) combined with 5-fluorouracil (5-Fu) on the treatment of human colorectal cancer in BALB/C nude mice s.c. xenograft model. Methods Effects of celecoxib combined 5-Fu on the proliferatic in xenograft carcinoma induced by HT-29 were investigated. Simultaneously the method of immunohistochem. and western blot were used to est. the expression of Cytochrome C, caspase-3 and caspase-9, the apoptosis morphous was detected by electron microscope and the apoptosis of tumor cell was detected by TUNEL to det. apoptotic index (AI). Results The effect of synergistic usage of 5-Fu and celecoxib for the treatment of human colorectal cancer was better than other groups. The resp. rates of the tumor inhibition of B group, C group and D group were 27.81%, 53.02%, 78.37%, and the differences compared with control group (0) were significant ($P < 0.01$). Compared with control group the apoptosis of tumor cell in treated groups notably raised and the statistical differences of the apoptotic index (AI) among treated groups were significant ($P < 0.01$). The means of fimmunohistochem. and western blot display that the expression of Cytochrome C, caspase-3 and caspase-9 of treated groups increased obviously compared with the control group. Meanwhile the statistical differences of the expression of Cytochrome C, caspase-3 and caspase-9 among the treated groups were also significant ($P < 0.05$). Conclusion Celecoxib and 5-Fu have resp. effect to inhibit the growth of tumor. Compared with celecoxib or 5-Fu individual drug group, Celecoxib combined with 5-Fu significantly inhibited the growth of human colorectal cancer in nude mice s.c. xenograft. The mechanism of antitumor maybe is correlate with inducing apoptosis and activation mitochondrion accommodation pathway by upregulating the expression of Cytochrome C, caspase-3 and caspase-9.

Answer 2:

Bibliographic Information

Combination Treatment of Human Umbilical Cord Matrix Stem Cell-Based Interferon-Beta Gene Therapy and 5-Fluorouracil Significantly Reduces Growth of Metastatic Human Breast Cancer in SCID Mouse Lungs. Rachakatla, Raja Shekar; Pyle, Marla M.; Ayuzawa, Rie; Edwards, Sarah M.; Marini, Frank C.; Weiss, Mark L.; Tamura, Masaaki; Troyer, Deryl. Department of Anatomy & Physiology, Kansas State University, Manhattan, KS, USA. Cancer Investigation (2008), 26(7), 662-670. Publisher: Informa Healthcare, CODEN: CINVD7 ISSN: 0735-7907. Journal written in English. AN 2008:923408 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Umbilical cord matrix stem (UCMS) cells that were engineered to express interferon-beta (IFN-β) were transplanted weekly for three weeks into MDA 231 breast cancer xenografts bearing SCID mice in combination with 5-fluorouracil (5-FU). The UCMS cells were found within lung tumors but not in other tissues. Although both treatments significantly reduced MDA 231 tumor area in the SCID mouse lungs, the combined treatment resulted in a greater redn. in tumor area than by either treatment used alone. These results indicate that a combination treatment of UCMS-IFN-β cells and 5-FU is a potentially effective therapeutic procedure for breast cancer.

Answer 3:

Bibliographic Information

Anti-tumor effect of angiogenesis inhibitor TNP-470 and 5-FU combined therapy on human gastric cancer xenograft.
Nishimura, Koji; Ohno, Masakazu; Chung-Kang, Cheng; Kuroda, Yoshikazu. Department of Gastroenterological Surgery, Graduate School of Medical Sciences, Kobe, Japan. Hepato-Gastroenterology (2008), 55(82-83), 774-778. Publisher: H.G.E. Update Medical Publishing S.A., CODEN: HEGAD4 ISSN: 0172-6390. Journal written in English. CAN 149:118997 AN 2008:746737 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background/Aims: TNP-470, an angiogenesis inhibitor, has already been used in combination with chemotherapy to enhance its antitumor activity. The mechanism of enhanced antitumor activity in combination therapy has not been clarified, however, and few studies have described the combined effect of TNP-470 and 5-fluorouracil (5-FU) on gastric cancer. The present study was conducted to investigate the effect of TNP-470 + 5-FU on gastric cancer cell line MKN-45 in vivo and in vitro. Methodol.: MKN-45 cells were s.c. injected into mice that were divided into 4 groups: a control group, a 5-FU treated group, a TNP-470 treated group, and a 5-FU + TNP-470 treated group. After the inoculation, the vol. of s.c. tumors was measured. Blood and lymphatic vessels were also analyzed for the assessment of lymphangiogenesis. Results: Compared with 5-FU or TNP-470 alone, the combined effect of TNP-470 and 5-FU significantly inhibited and suppressed tumor growth in a synergistic fashion. The combined therapy significantly suppressed both angiogenesis and lymphagenesis. Conclusions: The study suggests that the combined therapy provides an enhanced antitumor effect on human gastric cancer. The enhanced antitumor activity is explained mainly by the stronger inhibition of angiogenesis.

Answer 4:

Bibliographic Information

Anti-angiogenic effect of nitric oxide synthase inhibitor on colorectal cancer xenografts in nude mice. Sun, Wenzhou; Yu, Libo; Dong, Xinshu. The Affiliated Tumor Hospital, Harbin Medical University, Harbin, Heilongjiang Province, Peop. Rep. China. Shijie Huaren Xiaohua Zazhi (2007), 15(2), 114-117. Publisher: Shijie Weichangbingxue Zazhishe, CODEN: SHXZF2 ISSN: 1009-3079. Journal written in Chinese. CAN 149:715 AN 2008:426091 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anti-angiogenic effect of N G-nitro-L-arginine Me ester (L-NAME), an inhibitor of nitric oxide synthase on the growth of colorectal cancer xenografts in nude mice was investigated. The xenografts derived from colorectal carcinoma cells LS174 were inoculated in nude mice, and then mice were randomly divided into group A, B, C and D, intragastrically treated with normal saline (n=6, 0.2 mL), L-NAME (n=6, 1.5 mg/kg), 5-fluorouracil (5-FU, n=6, 5 mg/kg), and L-NAME plus 5-FU (L-NAME 1.5 mg/kg and 5-FU 5 mg/kg), resp., for 2 wk (three times per wk). Tumor vol. was measured in nude mice bearing xenografts. The microvessel d. (MVD) was detd. by immunohistochem., and the protein level of vascular endothelial growth factor (VEGF) was detected by Western blot. The tumor inhibition rates were significantly higher in group B, C and D than that in group A (34.1%, 46.0% and 74.1% vs 0, $P<0.01$). There was significant difference between group B and D as well as between group C and D. The value of MVD in group A was 28.9 ± 2.7, markedly higher than that in group B (16.2 ± 3.1). The level of VEGF protein was also decreased in group B compared with that in group A (98.56 ± 1.76 vs 113.14 ± 2.34, $P<0.05$). L-NAME may restrain the growth of human colorectal carcinoma LS174 xenografts by inhibiting the angiogenesis in nude mice. L-NAME in combination with 5-FU may produce a synergetic effect.

Answer 5:

Bibliographic Information

Image-Guided Enzyme/Prodrug Cancer Therapy. Li, Cong; Penet, Marie-France; Winnard, Paul, Jr.; Artemov, Dmitri; Bhujwalla, Zaver M. Johns Hopkins University In Vivo Cellular Molecular Imaging Center Program, The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD, USA. Clinical Cancer Research (2008), 14(2), 515-522. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 149:118848 AN 2008:106216 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

PURPOSE: The success of enzyme/prodrug cancer therapy is limited by the uncertainty in the delivery of the enzyme in vivo. This study shows the use of noninvasive magnetic resonance (MR) and optical imaging to image the delivery of a prodrug enzyme. With this capability, prodrug administration can be timed so that the enzyme concn. is high in the tumor and low in systemic circulation and normal tissue, thereby minimizing systemic toxicity without compromising therapeutic efficiency. Exptl. Design: The delivery of a multimodal imaging reporter functionalized prodrug enzyme, cytosine deaminase, was detected by MR and optical imaging in MDA-MB-231 breast cancer xenografts. Stability of the enzyme in the tumor was verified by 19F MR spectroscopy, which detected conversion of 5-fluorocytosine to 5-fluorouracil. The optimal time window for prodrug injection detd. by imaging was validated by immunohistochem., biodistribution, and high-performance liq. chromatog. studies. The therapeutic effect and systemic toxicity of this treatment strategy were investigated by histol. studies and tumor/body wt. growth curves. RESULTS: The delivery of the functionalized enzyme in tumors was successfully imaged in vivo. The optimal time window for prodrug administration was detd. to be 24 h, at which time the enzyme continued to show high enzymic stability in tumors but was biodegraded in the liver. Significant tumor growth delay with tolerable systemic toxicity was obsd. when the prodrug was injected 24 h after the enzyme. CONCLUSION: These preclin. studies show the feasibility of using a MR-detectable prodrug enzyme to time prodrug administration in enzyme/prodrug cancer therapy.

Answer 6:

Bibliographic Information

Gene expression predicts differential capecitabine metabolism, impacting on both pharmacokinetics and antitumor activity. Guichard, Sylvie M.; Macpherson, Janet S.; Mayer, Iain; Reid, Eilidh; Muir, Morwenna; Dodds, Michael; Alexander, Susan; Jodrell, Duncan I. Cancer Research UK Pharmacology and Drug Development Group, Edinburgh Cancer Research Centre, University of Edinburgh, Edinburgh, UK. European Journal of Cancer (2008), 44(2), 310-317. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 149:167255 AN 2008:82554 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Capecitabine is converted into 5'-deoxy-5-fluorocytidine (5'DFCR), 5'-deoxy-5-fluorouridine (5'DFUR) and 5-fluorouracil (5-FU) by CES1 and 2, CDD, and TP, in both liver and tumor. 5-FU is catabolized by DPD. Gene expression anal. of these enzymes was undertaken in fresh human hepatocytes, mouse liver, colorectal cancer cell lines and xenografts. Cell lines with low CDD expression (<1.5) had 5'DFCR/5'DFUR cytotoxicity ratios >2 and cell lines with TP/DPD < 0.6 had 5'DFUR IC50 > 50 μM (SRB assay). A pharmacokinetic/pharmacodynamic study in nude mice bearing HCT 116 xenografts and treated with capecitabine by oral gavage assessed pharmacokinetic, gene expression and antitumor activity. Low liver CDD correlated with high 5'DFCR plasma concns. in mice. CDD expression was .apprx.100-fold higher in fresh human hepatocytes than mouse liver, explaining the higher plasma 5'DFUR concns. reported previously in humans. Tumor 5-FU concn. correlated with TP/DPD and with tumor response. These studies identify the potential utility of gene expression anal. and drug monitoring in tumor in patients.

Answer 7:

Bibliographic Information

Phase II trial of cetuximab in combination with fluorouracil, leucovorin, and oxaliplatin in the first-line treatment of metastatic colorectal cancer. Tabernero, Josep; Van Cutsem, Eric; Diaz-Rubio, Eduardo; Cervantes, Andres; Humblet, Yves; Andre, Thierry; Van Laethem, Jean-Luc; Soulie, Patrick; Casado, Esther; Versylpe, Chris; Valera, Javier Sastre; Tortora, Giampaolo; Ciardiello, Fortunato; Kisker, Oliver; de Gramont, Aimery. Medical Oncology Service, Vall d'Hebron University Hospital, Barcelona, Spain. Journal of Clinical Oncology (2007), 25(33), 5225-5232. Publisher: American Society of Clinical Oncology, CODEN: JCONDN ISSN: 0732-183X. Journal written in English. CAN 148:253533 AN 2007:1464324 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose:This phase II study investigated the efficacy and safety of cetuximab combined with std. oxaliplatin-based chemotherapy (infusional fluorouracil, leucovorin, and oxaliplatin [FOLFOX-4]) in the first-line treatment of epidermal growth factor receptor-expressing metastatic colorectal cancer (mCRC). Patients and Methods: The activity of cetuximab plus oxaliplatin was investigated in colon cancer cell lines and xenograft models. In the clin. study, patients with mCRC received on day 1 of a 14 day cycle, cetuximab (initial dose 400 mg/m2 during week 1, then 250 mg/m2 weekly) followed by FOLFOX-4 (oxaliplatin 85 mg/m2 on day 1; leucovorin 200 mg/m2 on days 1 and 2, followed by fluorouracil 400 mg/m2 bolus then 600 mg/m2 i.v. infusion during 22 h on days 1 and 2). Results: The preclin. studies confirmed the supra-additive activity of cetuximab to oxaliplatin. In the clin. study, 43 patients were included, with a median age of 65 years (range, 43 to 78 years). Response rates (RRs) were 79% (unconfirmed) and 72% (confirmed), with 95% disease control. Median progression-free survival (mPFS) and median duration of response were 12.3 and 10.8 mo, resp. Ten patients (23%) underwent resection with curative intent of previously unresectable metastases. After a median follow-up of 30.5 mo, median overall survival (mOS) was 30.0 mo. Cetuximab did not increase the characteristic toxicity of FOLFOX-4 and was generally well tolerated. Conclusion: Cetuximab in combination with FOLFOX-4 is a highly active first-line treatment for mCRC, showing encouraging RR, mPFS, and mOS values. The treatment resulted in a high resectability rate, which could potentially result in an improved cure rate. This combination is under phase III development.

Answer 8:

Bibliographic Information

Combination of ZD55-MnSOD therapy with 5-FU enhances antitumor efficacy in colorectal cancer. Zhang, Yiqun; Qin, Xinyu; Zhang, Yanhong; Zhao, Lili; Wang, Yigang; Liu, Xinyuan; Yao, Liqing. Department of General Surgery, Zhongshan Hospital of Fudan University, Shanghai, Peop. Rep. China. Journal of Cancer Research and Clinical Oncology (2008), 134(2), 219-226. Publisher: Springer, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 148:552879 AN 2007:1406196 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: ZD55-MnSOD is an E1B 55 kDa-deleted replication-competent adenovirus and armed with the therapeutic gene MnSOD. The expression of the therapeutic gene MnSOD increases with the selective replication of the oncolytic adenovirus (ZD55) so that ZD55-MnSOD has more significant activity than the replicate defective adenovirus Ad-MnSOD in vitro and in vivo. The tumor cannot be completely eradicated only with ZD55-MnSOD, although ZD55-MnSOD has obvious antitumor activity. 5-fluorouracil (5-FU) is still the most effective adjuvant therapy for patients with colorectal cancer. Methods: We reasoned that combined treatment of cancer cells with ZD55-MnSOD and 5-FU might have a synergistic effect. In vitro expts. with SW620 colorectal carcinoma cell line demonstrated that it was sensitive to ZD55-MnSOD, esp. most sensitive to ZD55-MnSOD plus 5-FU treatment. Treatment with both ZD55-MnSOD and 5-FU could induce more significant apoptosis in cancer cells compared with ZD55-MnSOD or 5-FU alone, resp. A better antitumor activity was obsd. by ZD55-MnSOD plus 5-fluorouracil (5-FU) treatment. Tumor growth was greatly inhibited by this combined treatment, and animal survival time increased. Conclusion: These results show that, by using the combination therapies, a significant decrease in tumor mass can be achieved, which suggest that ZD55-MnSOD in combination with 5-FU may have potential clin. implications.

Answer 9:

Bibliographic Information

The effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 in human breast cancer xenograft (MCF-7) transplanted in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Lv, Ya-lei; Wang, Shu-qin. Department of Medical Oncology, The 4th Hospital of Hebei Medical University, Shijiazhuang, Peop. Rep. China. Linchuang Zhongliuxue Zazhi (2007), 12(3), 173-176. Publisher: Institution of Chinese Clinical Oncology Journal, CODEN: LZZIA5 ISSN: 1009-0460. Journal written in Chinese. CAN 148:205626 AN 2007:1152600 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The objective of the paper is to investigate the effects of various chemotherapy regimens on the expression of PCNA and Bcl-2 of breast cancer, to assess the relationships between chemotherapy and two markers, and to evaluate the value of them to predict the response of chemotherapy. Forty-eight nude mice models of human breast cancer xenograft (MCF-7) were established, and then were randomly divided into control and 5 chemotherapy groups (each group, n = 8). Among 5 chemotherapy groups, mice were treated i.p. or orally by 5 chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) resp. at two-thirds LD10 (dose lethal to 10% of the mice). Control animals were administered i.p. with normal saline. The pathol. feature of transplanted tumor was studied by HE stain, and the expression of Bcl-2 and PCNA was studied by SP immunohistochem. method. The expression of PCNA in 5 chemotherapy group was significantly lower than that of control ($P<0.05$), and the expression of PCNA in NP, TP and Xeloda groups was significantly lower than that of CMF and CAF groups ($P<0.05$). Moreover, the expression of PCNA was significantly correlated with pathol. therapeutic response ($P=0.001$). The expression of Bcl-2 in CAF, NP, TP, Xeloda groups was significantly higher than that of control ($P<0.05$). Moreover, the expression of Bcl-2 in TP group was significantly higher than that of CMF and CAF groups ($P<0.05$). The expression of Bcl-2 was not significantly correlated with the pathol. therapeutic response ($P=0.093$). Chemotherapy can increase the expression of PCNA, and decrease the expression of Bcl-2. Different chemotherapy regimens have different effects on PCNA and Bcl-2. PCNA can become a factor to evaluate the response to chemotherapy, and become possibly the prospective factor of chemoselect.

Answer 10:

Bibliographic Information

Mechanistic analysis and comparison of viral fusogenic membrane proteins for their synergistic effects on chemotherapy.
Hoffmann, Dennis; Grunwald, Thomas; Kuate, Seraphin; Wildner, Oliver. Department of Molecular and Medical Virology, Ruhr-University Bochum; Institute of Microbiology and Hygiene, Bochum, Germany. Cancer Biology & Therapy (2007), 6(4), 510-518. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479955 AN 2007:1039368 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previously we demonstrated that the expression of fusogenic membrane proteins (FMG) of measles virus (MV-H/F) can synergistically enhance chemotherapy. In this study, we used median-effect anal. to evaluate whether the expression of respiratory syncytial virus (RSV-F), as well as vesicular stomatitis virus (VSV-G) can also synergistically enhance chemotherapy. Furthermore we elucidated by western blot anal. some mol. pathways that might be responsible for this effect. We showed in colorectal cancer cell lines that the expression of MV-H/F, but also of RSV-F, as well as VSV-G can synergistically enhance p53-independent clin. relevant chemotherapy (FOLFOX) over most of the cytotoxic dose range. In a s.c. HT-29 colorectal xenograft model, we demonstrated that the administration of replication-deficient adenovirus vectors encoding MV-H/F, RSV-G or VSV-G in combination with FOLFOX significantly enhanced treatment outcome when compared to the treatment with each compd. individually. The anti-neoplastic efficacy of RSV-F was somewhat better than that of MV-H/F and both were statistically significantly more efficacious than VSV-G alone or in combination with chemotherapy. Treatment efficacy was further significantly improved when the replication-deficient FMG encoding vectors were trans-complemented for replication with a replication-restricted oncolytic adenovirus to improve tumor transduction efficiency. The combination of FMG expression, chemotherapy and trans-complementing oncolytic vectors resulted in a significantly better treatment efficacy than treatment with its components as single- or double-agent therapy. Our data indicates that FMG expression (i.e., RSV-F and MV-H/F) in combination with chemotherapy and viral oncolysis warrants further investigations.

Answer 11:

Bibliographic Information

Clinical and mechanistic aspects of glucocorticoid-induced chemotherapy resistance in the majority of solid tumors.
Zhang, Chengwen; Wenger, Till; Mattern, Juergen; Ilea, Septimia; Frey, Christian; Gutwein, Paul; Altevogt, Peter; Bodenmueller, Wolfram; Gassler, Nikolaus; Schnabel, Philipp A.; Dienemann, Hendrik; Marme, Alexander; Hohenfellner, Markus; Haferkamp, Axel; Pfitzenmaier, Jesco; Groene, Hermann-Josef; Kolb, Armin; Buechler, Peter; Buechler, Markus W.; Friess, Helmut; Rittgen, Werner; Edler, Lutz; Debatin, Klaus-Michael; Krammer, Peter H.; Rutz, Hans P.; Herr, Ingrid. Research Group Molecular OncoSurgery,

University of Heidelberg, Heidelberg, Germany. Cancer Biology & Therapy (2007), 6(2), 278-287. Publisher: Landes Bioscience, CODEN: CBTAAO ISSN: 1538-4047. Journal written in English. CAN 147:479951 AN 2007:1039338 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Glucocorticoids have been used widely in conjunction with cancer therapy due to their ability to induce apoptosis in hematol. cells and to prevent nausea and emesis. However, recent data including ours, suggest induction of therapy-resistance by glucocorticoids in solid tumors, although it is unclear whether this happens only in few carcinomas or is a more common cell type specific phenomenon. We performed an overall statistical anal. of our new and recent data obtained with 157 tumor probes evaluated in vitro, ex vivo and in vivo. The effect of glucocorticoids on apoptosis, viability and cell cycle progression under diverse clin. important questions was examd. New in vivo results demonstrate glucocorticoid-induced chemotherapy resistance in xenografted prostate cancer. In an overall statistical anal. we found glucocorticoid-induced resistance in 89% of 157 analyzed tumor samples. Resistance is common for several cytotoxic treatments and for several glucocorticoid-derivs. and due to an inhibition of apoptosis, promotion of viability and cell cycle progression. Resistance occurred at clin. achievable peak plasma levels of patients under anti-emetic glucocorticoid therapy and below, lasted for a long time, after one single dose, but was reversible upon removal of glucocorticoids. Two nonsteroidal alternative anti-emetic agents did not counteract anticancer treatment and may be sufficient to replace glucocorticoids in cotreatment of carcinoma patients. These data demonstrate the need for prospective clin. studies as well as for detailed mechanistic studies of GC-induced cell-type specific pro- and anti-apoptotic signaling.

Answer 12:

Bibliographic Information

Antitumor activity of a combination of trastuzumab (Herceptin) and oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2-overexpressing pancreatic cancer. Saeki, Hiroyuki; Yanoma, Shunsuke; Takemiya, Shouji; Sugimasa, Yukio; Akaike, Makoto; Yukawa, Norio; Rino, Yasushi; Imada, Toshio. Department of General Surgery, Yokohama City University, 3-9 Hukuura, Kanazawa-ku, Yokohama, Kanagawa, Japan. Oncology Reports (2007), 18(2), 433-439. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 147:398030 AN 2007:955678 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxic effect of trastuzumab in combination with oral fluoropyrimidine S-1 on human epidermal growth factor receptor 2 (HER2)-overexpressing human pancreatic cancer cell line TRG in vitro and in vivo was investigated. HER2 expression in TRG was analyzed by RT-PCR and flow cytometry. For in vitro expts., 5-fluorouracil (5-FU) was used instead of S-1. In vivo studies were conducted with TRG xenografts in athymic mice. Trastuzumab (10 mg/kg) was administered i.p. once a week for 4 wk. S-1 (10 mg/kg) was administered orally 5 days a week for 4 wk. The results showed that TRG cells were pos. for HER2 mRNA and overexpressed HER2 protein. Either trastuzumab or 5-FU concn.-dependently inhibited the growth of TRG cells. The combination of trastuzumab and 5-FU resulted in a significant inhibition of growth of TRG cells compared to either agent alone ($P<0.001$). Incubation of TRG cells with peripheral blood mononuclear cells after treatment with trastuzumab enhanced the antiproliferative effect of trastuzumab, which could be the result of antibody-dependent cellular cytotoxicity. The combination of trastuzumab and S-1 resulted in a significant redn. in xenograft vol. compared to each agent alone ($P<0.0001$). In conclusion, this study showed that combination therapy with trastuzumab and S-1 may be effective for HER2-overexpressing pancreatic cancer patients.

Answer 13:

Bibliographic Information

Effects of targeting magnetic drug nanoparticles on human cholangiocarcinoma xenografts in nude mice. Tang, Tao; Zheng, Jian-Wei; Chen, Bo; Li, Hong; Li, Xi; Xue, Ke-Ying; Ai, Xing; Zou, Sheng-Quan. Department of General Surgery, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Peop. Rep. China. Hepatobiliary &

Pancreatic Diseases International (2007), 6(3), 303-307. Publisher: First Affiliated Hospital, Zhejiang University School of Medicine, CODEN: HPDIAJ ISSN: 1499-3872. Journal written in English. CAN 147:197009 AN 2007:766382 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Targeting is a new therapeutic tool for malignant tumor as a result of combining nanotechnol. with chemotherapeutics. The aim of our study was to investigate the effects of magnetic nanoparticles enveloping a chemotherapeutic drug on human cholangiocarcinoma xenografts in nude mice. The human cholangiocarcinoma xenograft model was established in nude mice with the QBC939 cell line. The nude mice were randomly assigned to 7 groups. 0.9% Saline or magnetic nanoparticles, including high (group 2), medium (group 4) and low (group 5) dosages, were given to nude mice through the tail vein 20 days after the QBC939 cell line was implanted. Calcns. were made 35 days after treatment in order to compare the vols., inhibition ratios and growth curves of the tumors in each group. Mice in each group were sacrificed randomly to collect tumor tissues and other organs for electron microscopy and pathol. examn. The high and medium dosage groups were significantly different from the control group ($P < 0.05$). The tumor inhibition ratios for the high, medium and low dosage groups were 39.6%, 14.6% and 7.9%, resp. The tumor growth curve of groups 5, 4, and 2 changed slowly in turn. The high and medium groups showed cell apoptosis under an electron microscope. Magnetic nanoparticles can inhibit the growth of human cholangiocarcinoma xenografts in nude mice.

Answer 14:

Bibliographic Information

Astragalus saponins induce growth inhibition and apoptosis in human colon cancer cells and tumor xenograft. Tin, Mandy M. Y.; Cho, Chi-Hin; Chan, Kelvin; James, Anthony E.; Ko, Joshua K. S. Pharmacology and Toxicology Laboratory, School of Chinese Medicine, Hong Kong Baptist University, Kowloon Tong, Hong Kong, Peop. Rep. China. Carcinogenesis (2007), 28(6), 1347-1355. Publisher: Oxford University Press, CODEN: CRNGDP ISSN: 0143-3334. Journal written in English. CAN 147:63420 AN 2007:724579 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Astragalus memebranaceus is used as immunomodulating agent in treating immunodeficiency diseases and to alleviate the adverse effects of chemotherapeutic drugs. In recent years, it has been proposed that Astragalus may possess anti-tumorigenic potential in certain cancer cell types. In this study, the anti-carcinogenic effects of Astragalus saponin ext. were investigated in HT-29 human colon cancer cells and tumor xenograft. Our findings have shown that Astragalus saponins (AST) inhibit cell proliferation through accumulation in S phase and G2/M arrest, with concomitant suppression of p21 expression and inhibition of cyclin-dependent kinase activity. Besides, AST promotes apoptosis in HT-29 cells through caspase 3 activation and poly(ADP-ribose) polymerase cleavage, which is indicated by DNA fragmentation and nuclear chromatin condensation. Nevertheless, we also demonstrate the anti-tumorigenic effects of AST in vivo, of which the redn. of tumor vol. as well as pro-apoptotic and anti-proliferative effects in HT-29 nude mice xenograft are comparable with that produced by the conventional chemotherapeutic drug 5-fluorouracil (5-FU). In addn., the side effects (body wt. drop and mortality) assocd. with the drug combo 5-FU and oxaliplatin are not induced by AST. These results indicate that AST could be an effective chemotherapeutic agent in colon cancer treatment, which might also be used as an adjuvant in combination with other orthodox chemotherapeutic drugs to reduce the side effects of the latter compds.

Answer 15:

Bibliographic Information

The histone deacetylase inhibitor PXD101 synergizes with 5-fluorouracil to inhibit colon cancer cell growth in vitro and in vivo. Tumber, Anthony; Collins, Laura S.; Petersen, Kamille Dumong; Thougaard, Annemette; Christiansen, Sanne J.; Dejligbjerg, Marielle; Jensen, Peter Buhl; Sehested, Maxwell; Ritchie, James W. A. TopoTarget UK LTD, Abingdon, UK. Cancer Chemotherapy and Pharmacology (2007), 60(2), 275-283. Publisher: Springer, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 147:268549 AN 2007:510771 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Histone deacetylase inhibitors (HDACi) inhibit the growth of cancer cells, and combinations of HDACi with established chemotherapeutics can lead to synergistic effects. We have investigated effects of PXD101 (HDACi in phase II clin. trials) in combination with 5-fluorouracil, on tumor cell proliferation and apoptosis both in vitro and in vivo. HCT116 cells were studied using proliferation and clonogenic assays. Synergistic inhibition of proliferation and clonogenicity was detd. by incubation with PXD101 and 5-fluorouracil, and anal. using CalcuSyn software. The effect of combining PXD101 and 5-fluorouracil on apoptosis was examd. in vitro using PARP-cleavage and TUNEL. Finally, the effectiveness of combining PXD101 and 5-fluorouracil in vivo was tested using both HT-29 and HCT116 xenograft models. Synergistic inhibition of proliferation and clonogenicity was obtained when HCT116 cells were incubated with PXD101 and 5-fluorouracil. 5-fluorouracil combined with PXD101 also increased DNA fragmentation and PARP cleavage in HCT116 cells. Incubation with PXD101 down regulated thymidylate synthase expression in HCT116 cells. In vivo studies, using mouse HT29 and HCT116 xenograft models, showed improved redns. in tumor vol. compared to single compd., when PXD101 and 5-fluorouracil were combined. PXD101 and 5-fluorouracil synergistically combine in their antitumor effects against colon cancer cells in vitro and show enhanced activity when combined in vivo. Based on the results presented herein, a rationale for the use of PXD101 and 5-fluorouracil in combination in the clinic has been demonstrated.

Answer 16:

Bibliographic Information

Predictive value of GADD153, p21 and c-Jun for chemotherapy response in gastric cancer. Akatsu, Yukako; Saikawa, Yoshiro; Kubota, Tetsuro; Akatsu, Tomotaka; Yoshida, Masashi; Kitagawa, Yuko; Otani, Yoshihide; Kumai, Koichiro; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, 35 Shinanomachi Shinjuku Tokyo, Japan. Cancer Science (2007), 98(5), 707-715. Publisher: Blackwell Publishing Asia Pty Ltd., CODEN: CSACCM ISSN: 1347-9032. Journal written in English. CAN 147:28281 AN 2007:490784 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We sought to det. whether changes in the expression of early response genes (GADD153, p21 and c-Jun) are indicators of chemotherapy response in gastric cancer. Three human gastric cancer cell lines were exposed to 5-fluorouracil or cisplatin in vitro. Xenografts of TMK-1 cells in nude mice were also treated with 5-fluorouracil or cisplatin in vivo. For each of these treatments, we tested for a correlation between early gene expression levels and inhibition ratios derived at a later time. A 5-fluorouracil deriv., 5-1, and cisplatin were administered to 12 patients with advanced gastric cancer for 3 wk. Gene expression levels were measured using biopsy specimens obtained by endoscopy soon after initiation of chemotherapy. There was a significant correlation between expression levels of these genes at 24 h and inhibition ratios at 72 h in vitro. Cut-off values detd. from receiver-operating characteristic curves were 1.3 for GADD153, 1.8 for p21 and 2.1 for c-Jun There was also a significant correlation between gene expression levels at 2 days inhibition ratios at 21 days in vivo. Cut-off values were 1.8 for GADD153, 1.9 for p21 and 2.2 for c-Jun. Levels of early response gene expression in patients showing progressive disease were significantly lower than those in patients with partial response. Changes in the expression of the three early response genes soon after drug administration could improve predictions of the final outcome of chemotherapy in gastric cancer.

Answer 17:

Bibliographic Information

Effects of various chemotherapy regimens on the expression of PCNA and growth of human breast cancer xenograft (MCF-7) in nude mice. Wang, Yu-dong; Liu, Wei; Ji, Zhi-min; Zhang, Zhi-gang; Wang, Jun-ling; Yan, Xia; Zhang, Xiang-hong. Department of Medical Oncology, 4th Hospital, Hebei Medical University, Shijiazhuang Hebei, Peop. Rep. China. Zhongguo Aizheng Zazhi (2007), 17(2), 139-143. Publisher: Fudan Daxue Fushu Zhongliu Yiyuan, CODEN: ZAZHAF ISSN: 1007-3639. Journal written in Chinese. CAN 147:86596 AN 2007:395164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although standardized therapy has been widely adapted in clin. practice and results are being improved, effective protocols for truly individualized chemotherapy is still lacking. The anti-tumor activity of different combination regimens on human breast cancer xenograft (MCF-7) transplanted in nude mice and their impacts on the expression of PCNA were investigated, and to evaluate the value of PCNA as predictive factors for the res. 88 Nude mice with human breast cancer xenograft (MCF-7) were randomly divided into control and 10 chemotherapy groups, and 8 mice were assigned into each group. Among 5 chemotherapy groups, they were treated either i.p. or orally by 5 different combinations of chemotherapy regimens (CMF, CAF, NP, TP, Xeloda) at one-third of LD10 dosage, and another 5 chemotherapy groups were treated at two-third . Control animals were given normal saline i.p. The body wt. of nude mice and transplanted tumor growth were recorded on a regular basis, and tumor growth inhibition was calcd. The pathol. features of the transplanted tumor were studied under the microscope before and after treatment. The expression of PCNA was evaluated by SP immunohistochem. method and flow cytometry. The results show that body wt. and tumor wt. of nude mice treated by two-third LD10 dosage of various chemotherapy combinations were significantly lower than that in the control ($P<0.05$), and the inhibition rate of tumor growth for the groups we. The results showed that the two-third LD10 dosage of chemotherapy could reflect the anti-tumor effect of various combinations chemotherapy better and more accurately, so this dosage was used for the next study. The expression at PCNA by immunohistochem. studies shows that the expression of PCNA in every chemotherapy group was significantly lower than that of the control ($P<0.05$).

Moreover, the expressions of PCNA in NP group was significantly lower than that of CMF, CAF, TP and Xeloda group ($P<0.05$), while TP and Xeloda group was significantly lower than that of CMF and CAF group ($P<0.05$). FCM anal. shows that FI value of PCNA in every chemotherapy group was significantly lower than that of the control ($P<0.05$). FI value of PCNA in TP and Xeloda group was significantly lower than that of CMF and CAF group ($P<0.05$), while NP group a significantly lower than that of CMF group ($P<0.05$). Relationship between PCNA expression and pathol. response shows that the expression of PCNA was pos. correlated with pathol. therapeutic response of transplanted breast carcinoma ($r=0.540$, $P<0.05$). It was concluded that in vivo chemosensitivity testing with two third LD10 dosage of various combinations of chemotherapy cancer could somewhat predict the clin. situations. All of various chemotherapy regimens can decrease the expression of PCNA in breast cancer. The expression of PCNA could perhaps serve as the factor to judge the response to chemotherapy, and play a role in the selection of the kind of chemotherapy to be used in the clinic.

Answer 18:

Bibliographic Information

Antitumor activity of combination treatment of Lentinus edodes mycelium extracts with 5-fluorouracil against human colon cancer cells xenografted in nude mice. Wu, Chih-Hsiung; Wu, Chi-Chen; Ho, Yuan-Soon. Department of Surgery, School of Medicine, Taipei Medical University and Hospital, Taipei, Taiwan. Journal of Cancer Molecules (2007), 3(1), 15-22. Publisher: MedUnion Press, CODEN: JCMOCF ISSN: 1816-0735. Journal written in English. CAN 146:266125 AN 2007:278113 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (5-FU) is one of the widely used chemotherapeutic drugs targeting various cancers, but its chemoresistance remains as a major obstacle in clin. settings. In this study, we evaluated the in vivo efficacy of Lentinus edodes mycelium exts. (designated as LEM), an edible mushroom exts., as a 5-FU adjuvant agent. Furthermore, we intended to study the underlying mechanisms to account for the role of LEM. Human colon cancer COLO 205 cells were treated with 5-FU, LEM, or combination of 5-FU with LEM. Induction of apoptosis and cell cycle arrest was demonstrated by DNA ladder electrophoresis and flow cytometry, resp. Addnl., COLO 205 cells were transplanted into athymic nude mice as a tumor model for evaluation of the antitumor effect of combination treatment with LEM plus 5-FU. The mechanisms for altered cell cycle progression were investigated by immunoblotting analyses of the G0/G1-phase regulatory proteins. COLO 205 cells were markedly sensitized to apoptosis and G0/G1-phase arrest by combination treatment of 5-FU with LEM when compared with 5-FU alone. Our results furthermore indicated that LEM markedly enhanced the 5-FU-mediated upregulation of the p53, p21/Cip1 and p27/Kip1 proteins in COLO 205 cells-xenografted tumor tissues. In contrast, although the expression levels of cyclins B and D3 proteins were down regulated in the 5-FU-treated tumor tissues, no significant potentiation effect was obsd. in the tumors with 5-FU and LEM combination treatment. Our results suggest that combination of 5-FU with LEM may represent a novel chemotherapeutic strategy in colon cancers and that p53, p21/Cip1 and p27/Kip1 may play some important roles for the involvement in antitumor activity.

Answer 19:

Bibliographic Information

Efficacy of gene therapy-delivered cytosine deaminase is determined by enzymatic activity but not expression. Dubois, L.; Dresselaers, T.; Landuyt, W.; Paesmans, K.; Mengesha, A.; Wouters, B. G.; Van Hecke, P.; Theys, J.; Lambin, P. Department of Radiation Oncology, GROW Research Institute, University of Maastricht, Maastricht, Neth. British Journal of Cancer (2007), 96(5), 758-761. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 147:63555 AN 2007:245111 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The potential utility of tumor-selective 5-fluorouracil treatment using attenuated Salmonella serovar typhimurium recombinant for cytosine deaminase (TAPET-CD) has been documented in exptl. settings. The present data demonstrate that in vivo 19F-magnetic resonance spectroscopy measurements allow the outcome prediction of this prokaryotic-based therapy, demonstrating the necessity of non-invasive real-time imaging techniques for treatment monitoring.

Answer 20:

Bibliographic Information

Changes to the dihydropyrimidine dehydrogenase gene copy number influence the susceptibility of cancers to 5-FU-based drugs: Data mining of the NCI-DTP data sets and validation with human tumour xenografts. Kobunai, Takashi; Ooyama, Akio; Sasaki, Shin; Wierzba, Konstanty; Takechi, Teiji; Fukushima, Masakazu; Watanabe, Toshiaki; Nagawa, Hirokazu. Department of Systematic Clinical Oncology, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan. European Journal of Cancer (2007), 43(4), 791-798. Publisher: Elsevier Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 147:1058 AN 2007:213726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Patient response to the anti-tumor drug 5-fluorouracil (5-FU) is variable, but predicting the response rate is important for the selection of effective chemotherapy. Our aim was to identify alterations in DNA copy no. that influence susceptibility of cancer cells to 5-FU-based drugs. The NCI public database was used to identify chromosome loci assocd. with drug sensitivity and DNA copy no. One of the 11 candidates, the cytogenetic band 1p21.3, harbors the dihydropyrimidine dehydrogenase (DPD) gene. To validate this finding, the DPD copy no. and in vivo sensitivity to 5-FU-based drugs were detd. in 31 human tumor xenografts. Those xenografts demonstrating low sensitivity had significantly higher DPD copy nos. than highly sensitive tumors ($P < 0.002$). Moreover, DPD mRNA expression levels were significantly correlated with DPD copy nos. ($P < 0.046$). An assessment of copy no. may be a more precise method of predicting the sensitivity of cancer patients to 5-FU related drugs.

Answer 21:

Bibliographic Information

S-1, an oral fluoropyrimidine, enhances radiation responses of DLD-1/FU human colon cancer xenografts resistant to 5-FU. Nakata, Eiko; Fukushima, Masakazu; Takai, Yoshihiro; Nemoto, Kenji; Ogawa, Yoshihiro; Nomiya, Takuma; Nakamura, Yasuhiro; Milas, Luka; Yamada, Shogo. Tohoku University Biomedical Engineering Research Organization, 2-1 Seiryocho Aobaku Sendai-City, Miyagi, Japan. Oncology Reports (2006), 16(3), 465-471. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 146:243291 AN 2006:902298 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

S-1, a novel oral fluoropyrimidine, is increasingly used for the treatment of human cancer including gastrointestinal carcinomas. Using

the 5-FU resistant DLD-1/FU human colon cancer cell xenografts, the present study investigated whether S-1 enhances the therapeutic efficacy of radiation and if so what are the underlying mechanisms. Nude mice bearing tumor xenografts were treated with radiation, S-1, or both. Tumor growth delay was the treatments' endpoint. To det. whether S-1 enhances intrinsic cell radiosensitivity, we performed clonogenic cell survival assay. Also we assessed the expression of thymidylate synthase (TS) using immunohistochem. assay. While S-1 or 5 Gy were only slightly effective as single agents in delaying tumor growth, the combined treatment was highly effective. Clonogenic cell survival showed that S-1 strongly enhanced cell radiosensitivity. Immunohistochem. showed that the expression of TS was down-regulated in tumors treated by S-1 plus radiation. Combined S-1 plus radiation treatment resulted in a synergistic effect in the therapy of 5-FU resistant human colon carcinoma xenografts (EF=2.06). The effect could be attributed to the ability of S-1 to increase cell radiosensitivity (EF=1.9) and to the down-regulation of TS involved in cellular processes leading to radio- and (or) chemo-resistance.

Answer 22:

Bibliographic Information

TIP30 inhibits growth of HCC cell lines and inhibits HCC xenografts in mice in combination with 5-FU. Zhao, Jian; Zhang, Xia; Shi, Mei; Xu, Hao; Jin, Jun; Ni, Haidong; Yang, Silei; Dai, Jianxin; Wu, Mengchao; Guo, Yajun. International Joint Cancer Institute & Eastern Hospital of Hepatobiliary Surgery, Second Military Medical University, Shanghai, Peop. Rep. China. Hepatology (Hoboken, NJ, United States) (2006), 44(1), 205-215. Publisher: John Wiley & Sons, Inc., CODEN: HPTLD9 ISSN: 0270-9139. Journal written in English. CAN 146:92773 AN 2006:751077 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Hepatocellular carcinoma (HCC) is an aggressive cancer with a poor prognosis. The specific cellular gene alterations responsible for hepatocarcinogenesis are not well known. Previous works showed that loss of TIP30, also called CC3, a putative tumor suppressor, increased the incidence of hepatocellular carcinoma in mice, and some clin. samples of human HCC tissues had aberrant expression of TIP30. Here, we report that the introduction of TIP30 by an adenovirus vector into HCC cell lines that had decreased expressions of TIP30 inhibited cell proliferation, decreased anchorage-dependent growth, suppressed invasion through the extracellular matrix, and inhibited tumorigenesis in nude mice. Moreover, exogenous expression of Tip30 sensitized HCC cells to cytotoxic drugs and to apoptosis induced by tumor necrosis factor-related ligands in vitro. Ectopic expression of TIP30 in HCC cells enhanced p53 expression and decreased Bcl-2/Bcl-xL expression. Treatment of nude mice bearing s.c. established HCC tumors with a combination of an adenovirus expressing TIP30 and the cytotoxic drug 5-fluorouracil completely suppressed tumor growth and prolonged survival. In conclusion, TIP30 may play an important role in the suppression of hepatocarcinogenesis by acting as a tumor suppressor. Overexpression of TIP30 might be a promising candidate as a treatment for HCC that would increase sensitivity to chemotherapeutic drugs.

Answer 23:

Bibliographic Information

Antitumor efficacy of edotecarin as a single agent and in combination with chemotherapy agents in a xenograft model. Ciomei, Marina; Croci, Valter; Ciavolella, Antonella; Ballinari, Dario; Pesenti, Enrico. Department of Biology, Drug Discovery Oncology, Nerviano Medical Sciences, Milan, Italy. Clinical Cancer Research (2006), 12(9), 2856-2861. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 145:388833 AN 2006:532561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The novel indolocarbazole edotecarin (J-107088, formerly ED-749) differs from other topoisomerase I inhibitors both pharmacokinetically and pharmacodynamically. In vitro, it is more potent than camptothecins and has a variable cytotoxic activity in 31 different human cancer cell lines. Edotecarin also possesses greater than additive inhibitory effects on cell proliferation when used in combination with other agents tested in vitro against various cancer cell lines. The present in vivo studies were done to extend the

in vitro findings to characterize the antitumor effects of edotecarin when used either alone or in combination with other agents (i.e., 5-fluorouracil, irinotecan, cisplatin, oxaliplatin, and SU11248) in the HCT-116 human colon cancer xenograft model. Treatment effects were based on the delay in onset of an exponential growth of tumors in drug-treated vs. vehicle control-treated groups. In all studies, edotecarin was active both as a single agent and in combination with other agents. Combination therapy resulted in greater than additive effects, the extent of which depended on the specific dosage regimen. Toxicity in these expts. was minimal. Of all 359 treated mice, the six that died of toxicity were in the high-dose edotecarin/oxaliplatin group. The results suggest that edotecarin may serve as effective chemotherapy of colon cancer when used as a single agent, in combination with std. regimens and other topoisomerase inhibitors or with novel agents, such as the multitargeted tyrosine kinase inhibitor SU11248.

Answer 24:

Bibliographic Information

Study of targeted and controlled release of 5-fluorouracil-loaded PLA nanoparticles and microspheres on treatment of gastric tumor. Ma, Chun-bao; Liu, Xiao-yan; Chang, Jin; Wang, Tao; Zhang, Qing-yu. Institute of Nanobiotechnology, School of Materials Sci. & Eng., Tianjin University, Tianjin, Peop. Rep. China. Nanoscience (2005), 1(1), 27-33. Publisher: American Association of Nanoscience and Technology, CODEN: NANODH ISSN: 1555-4880. Journal written in English. CAN 145:217552 AN 2006:357815 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The aim of this paper was to evaluate controlled release behavior and the therapeutic efficacy of 5-FU-loaded poly(lactic acid) (PLA) microspheres to human gastric cancer xenograft, and the targeting effect of VEGF/5-FU-loaded PLA nanoparticles. 5-FU-loaded PLA microspheres were prepd. by an emulsion evapn. method, and were characterized by SEM. 5-FU-loaded PLA nanoparticles were characterized by (TEM), and particle size analyzer detd. the distribution of nanoparticles size. The release performances of 5-FU microspheres in vitro were studied in PH 7.4 phosphate-buffered saline. The therapeutic efficacy of 5-FU-loaded PLA microspheres in vivo were studied using MGC-803 (human stomach cancer) xenograft. Thirty-two nude mice were divided into four groups (n = 8), 5-FU-loaded PLA microspheres were injected at tumor site. VEGF121 monoclonal antibody was connected with 5-FU-loaded PLA nanoparticles through carbodimide. The targeted effect of VEGF 5-FU-loaded nanoparticles in vivo were obsd. by single photon emission computed tomog. (SPECT) after tail vein injection at 1 h and 2 h. SEM observation showed that microspheres were spherical, and the diams. of two kinds of microspheres were 1 μm and 5 μm resp. The mean diam. of nanoparticles was 191.0 nm, and the index of polydispersity was 0.202. The drug was released following biphasic kinetics, initial burst and the following steady phase. 1μM and 5 μm 5-FU-loaded microspheres both resulted in increased life span (1 μm microspheres median survival time = 40.63 days, 5 μm microspheres median survival time = 62.25 days), against 5-FU pure drug (median survival time = 14.5 days). These results strongly suggest that 5-FU-loaded PLA microspheres increase life span of nude mice bearing MGC-803 tumors. After injection for 2 h, almost all the VEGF/5-FU-loaded PLA nanoparticles could centralize at the human gastric cancer xenograft sites.

That demonstrated VEGF monoclonal antibody remain its bioactivity after connection with nanoparticles, VEGF/5-FU-loaded PLA nanoparticles had very exact targeting function for gastric tumor xenograft.

Answer 25:

Bibliographic Information

Colony-Stimulating Factor-1 Antibody Reverses Chemoresistance in Human MCF-7 Breast Cancer Xenografts. Paulus, Patrick; Stanley, E. Richard; Schaefer, Romana; Abraham, Dietmar; Aharinejad, Seyedhossein. Laboratory for Cardiovascular Research, Department of Anatomy and Cell Biology, Vienna Medical University, Vienna, Austria. Cancer Research (2006), 66(8), 4349-4356. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 144:404857 AN 2006:350676 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of colony-stimulating factor-1 (CSF-1) and its receptor in breast cancer is correlated with poor prognosis. Based on

the hypothesis that blockade of CSF-1 would be beneficial in breast cancer treatment, we developed a murinized, polyethylene glycol-linked antigen-binding fragment (Fab) against mouse (host) CSF-1 (anti-CSF-1 Fab). Mice bearing human, chemoresistant MCF-7 breast cancer xenografts were treated with combination chemotherapy (CMF: cyclophosphamide, methotrexate, 5-fluorouracil; cycled twice i.p.), anti-CSF-1 Fab (i.p., cycled every 3 days for 14 days), combined CMF and anti-CSF-1 Fab, or with Ringer's soln. as a control. Anti-CSF-1 Fab alone suppressed tissue CSF-1 and retarded tumor growth by 40%. Importantly, in combination with CMF, anti-CSF-1 Fab reversed chemoresistance of MCF-7 xenografts, suppressing tumor development by 56%, down-regulating expression of the chemoresistance genes breast cancer-related protein, multidrug resistance gene 1, and glucosylceramide synthase, and prolonging survival significantly. Combined treatment also reduced angiogenesis and macrophage recruitment and down-regulated tumor matrix metalloproteinase-2 (MMP-2) and MMP-12 expression. These studies support the paradigm of CSF-1 blockade in the treatment of solid tumors and show that anti-CSF-1 antibodies are potential therapeutic agents for the treatment of mammary cancer.

Answer 26:

Bibliographic Information

Anti-angiogenic therapy and chemotherapy affect 99mTc sestamibi and 99mTc-HL91 accumulation differently in tumour xenografts. Kinuya, Seigo; Yokoyama, Kunihiko; Fukuoka, Makoto; Mori, Hirofumi; Shiba, Kazuhiro; Watanabe, Naoto; Shuke, Noriyuki; Michigishi, Takatoshi; Tonami, Norihisa. Department of Biotracer Medicine, Kanazawa University Graduate School of Medical Sciences, Japan. Nuclear Medicine Communications (2005), 26(12), 1067-1073. Publisher: Lippincott Williams & Wilkins, CODEN: NMCODC ISSN: 0143-3636. Journal written in English. CAN 144:225726 AN 2005:1169448 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Favorable effects of cytotoxic chemotherapy for tumors are characterized by the reduced accumulation of radiotracers such as 99mTc sestamibi (MIBI). Anti-angiogenic therapy is primarily cytostatic; consequently, its influence on tracer accumulation may differ from that of cytotoxic treatments. Methods: Anti-angiogenic therapy employing 2-methoxyestradiol was administered in mice bearing s.c. xenografts of LS180 colon cancer cells. The effects of chemotherapy with 5-fluorouracil were examd. as a cytotoxic counterpart. Treatments were conducted for 4 days from day 8. Distribution of 99mTc-MIBI and 99mTc-HL91, a hypoxic marker, was obsd. on days 8 and 12. Oxygen tension (PO2) in tumors was measured by a microelectrode. Cellular uptake of tracers was examd. in vitro in normoxic and hypoxic conditions. Results: 99mTc-MIBI accumulation decreased with increasing tumor wt. when no treatment was conducted. Tumor growth was suppressed by anti-angiogenic therapy and chemotherapy. 99mTc-MIBI accumulation in tumors decreased after chemotherapy as compared to pre-therapeutic values, whereas accumulation of 99mTc-HL91 increased. In contrast, accumulation of tracers did not significantly change after anti-angiogenic therapy as compared to that obsd. pre-therapeutically. Tumor PO2 decreased with increasing tumor vol. when no treatment was conducted. Chemotherapy reduced PO2 in tumors. PO2 in tumors treated with anti-angiogenic therapy was as high as that obsd. before treatment. 2-Methoxyestradiol or 5-fluorouracil did not significantly affect tracer accumulation in cells under both normoxic and hypoxic conditions in vitro. Conclusion: These findings indicate that scintigraphic assessment of therapeutic efficacy of anti-angiogenic therapy should be performed from a perspective distinct from that of cytotoxic treatment.

Answer 27:

Bibliographic Information

Simultaneous determination of capecitabine and its metabolites by HPLC and mass spectrometry for preclinical and clinical studies. Guichard, Sylvie M.; Mayer, Iain; Jodrell, Duncan I. Pharmacology and Drug Development Team, Cancer Research UK Centre, University of Edinburgh, Edinburgh, UK. Journal of Chromatography, B: Analytical Technologies in the Biomedical and Life Sciences (2005), 826(1-2), 232-237. Publisher: Elsevier B.V., CODEN: JCBAAI ISSN: 1570-0232. Journal written in English. CAN 143:378962 AN 2005:1105446 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A reverse-phase high-performance liq. chromatog. method with electrospray ionization and detection by mass spectrometry is described for the simultaneous detn. of capecitabine, its intermediate metabolites (DFCR, DFUR) and the active metabolite 5-fluorouracil in mouse plasma, liver and human xenograft tumors. The method was also cross-validated in human plasma and human tumor for clin. application. The method has greater sensitivity than previously published methods with an equiv. accuracy and precision. It uses less biol. material (plasma, tissue) and should therefore be applicable to biopsies in patients treated with capecitabine.

Answer 28:

Bibliographic Information

Establishment of enzyme-linked immunosorbent assay for quantification of orotate phosphoribosyltransferase in gastric carcinoma. Sakurai, Yoichi; Sakamoto, Kazuki; Sugimoto, Yoshikazu; Yoshida, Ikuo; Masui, Toshihiko; Tonomura, Shuhei; Inaba, Kazuki; Shoji, Mitsutaka; Nakamura, Yasuko; Uyama, Ichiro; Komori, Yoshiyuki; Ochiai, Masahiro; Matsuura, Shiro; Tanaka, Hideyuki; Oka, Toshinori; Fukushima, Masakazu. Dept. of Surgery, Fujita Health University School of Medicine, Japan. Gan to Kagaku Ryoho (2005), 32(7), 1017-1022. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 143:452069 AN 2005:810481 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A no. of enzymes have been shown to be involved in the process of activation and/or degrdn. of 5-fluorouracil, and they are potential candidates for predicting factors of chemosensitivity to 5-fluorouracil. Among them, orotate phosphoribosyltransferase (OPRT EC 2.4.2.10) is a key enzyme related to the first-step activation process of 5-fluorouracil and therefore it has been shown to be an important enzyme for the prediction of sensitivity to 5-fluorouracil and its related derivs. We developed a new ELISA system to accurately assess intratumoral activity of orotate phosphoribosyltransferase. A new sandwich ELISA system was established using anti-OPRT polyclonal antibodies obtained from the rabbit immunized with the recombinant human peptides of the OPRT mol. OPRT levels were measured in 8 human cancer xenografts transplanted in nude mice and 58 gastric cancer tissues using both a newly established ELISA and a conventional enzyme assay using radiolabeled 5-fluorouracil as a substrate. OPRT levels in 8 human cancer xenografts measured by this ELISA were significantly correlated with the OPRT enzyme activities (r2 = 0.782). Furthermore, OPRT activities measured in 58 gastric cancer tissues by enzyme assay were significantly correlated with those measured by the newly-established ELISA (r2 = 0.664). The ELISA system developed for the measurement of OPRT required a minimal amt. of carcinoma tissue samples, which could be an easy-of-use assay system to predict sensitivity to 5-fluorouracil in gastric carcinoma. These results suggest that this newly-developed sandwich ELISA system for the quantification of OPRT is tech. simple, feasible, and may be a useful tool to predict sensitivity to fluoropyrimidine-based anticancer chemotherapy in patients with gastric carcinoma and other cancers.

Answer 29:

Bibliographic Information

Combined effects of cantide and chemotherapeutic drugs on inhibition of tumor cells' growth in vitro and in vivo. Yang, Ying; Lv, Qiu-Jun; Du, Qing-You; Yang, Bing-Hu; Lin, Ru-Xian; Wang, Sheng-Qi. Beijing Institution of Radiation Medicine, Beijing, Peop. Rep. China. World Journal of Gastroenterology (2005), 11(16), 2491-2496. Publisher: World Journal of Gastroenterology, CODEN: WJGAF2 ISSN: 1007-9327. Journal written in English. CAN 143:109194 AN 2005:501149 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

AIM: To investigate the combination effect of hTERT antisense oligonucleotide "Cantide" and three chemotherapeutic drugs (cisplatin, 5-fluorouracil (5-FU) and adriamycin (ADM)) on inhibiting the proliferation of HepG2, BGC and A549 cell lines in vitro, and to investigate the efficacy of Cantide used in combination with cisplatin (DDP) in vivo. METHODS: Cantide was transfected into these tumor cells by Lipofectin, and cell growth activity was calcd. by microcytotoxicity assay. In vivo study, cells of HepG2 were implanted in Balb/c

nude mice for 4 d. Then Cantide, DDP and Cantide+DDP were given i.p. for 24 d resp. The body wts. of the tumor-bearing animals and their tumor mass were measured later to assess the effect of combination therapy in the nude mice. To evaluate the interaction of Cantide and these chemotherapeutic drugs, SAS software and Jin Zhengjun method were used. RESULTS: Combination treatments with 0.1 μmol/L Cantide reduced the IC50 of DDP, 5-FU and ADM from 1.07, 4.15 and 0.29 μg/mL to 0.25, 1.52 and 0.12 μg/mL resp. The inhibition ability of DDP, 5-FU and ADM resp. in combination with Cantide in these tumor cells was higher than that of these drugs alone ($P<0.0001$). And synergism ($Q \geq 1.15$) was obsd. at the lower concn. of DDP (≤ 1 μg/mL), 5-FU (≤10 μg/mL) and ADM (≤0.1 μg/mL) with combination of Cantide. In vivo, combination treatment with Cantide and DDP produced the greater growth inhibition of human liver carcinoma cells HepG2 in nude mice (0.65±0.19 g tumor) compared with that when only one of these drugs was used (Cantide group: 1.05±0.16 g tumor, $P = 0.0009<0.001$; DDP group: 1.13±0.09 g tumor, $P = 0.0001<0.001$). CONCLUSION: These findings indicate that Cantide may enhance therapeutic effectiveness of chemotherapeutic drugs over a wide range of tumor cells in vitro, and the combination use of Cantide and DDP can produce much higher inhibition rates, as compared with when either of these drugs was used only in vivo.

Answer 30:

Bibliographic Information

Chemosensitization by STI571 targeting the platelet-derived growth factor/platelet-derived growth factor receptor-signaling pathway in the tumor progression and angiogenesis of gastric carcinoma. Kim, Ryungsa; Emi, Manabu; Arihiro, Koji; Tanabe, Kazuaki; Uchida, Yoko; Toge, Tetsuya. International Radiation Information Center, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. Cancer (New York, NY, United States) (2005), 103(9), 1800-1809. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 143:19476 AN 2005:415435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Autocrine and paracrine growth mediated by the platelet-derived growth factor (PDGF)/PDGF receptor (PDGFR)-signaling pathway plays an important role in the progression of solid tumors. The authors assessed the effect of STI571 on the tumor growth of gastric carcinoma in combination with 5-fluorouracil (5-FU) or paclitaxel targeting the PDGF/PDGFR-signaling pathway. METHODS: In MKN-45 gastric carcinoma cells, the cytotoxic effect was evaluated by 3-(4,5 dimethiazol-2-yl)-2,5-diphenyl tetrazolium bromide assay, and the in vivo antitumor effect was evaluated in a nude mouse xenograft. Both STI571 and an antitumor drug were administered i.p. Gene expression was assessed by Western blot anal. and immunohistochem. staining. Apoptotic cell death was evaluated by the terminal deoxyuridine triphosphate-biotin nick-end labeling assay, and tumor angiogenesis was evaluated by microvessel d. anal. RESULTS: Treatment with STI571 alone was not effective in vitro, as assessed by a 50% inhibitory concn. value of 24.3 μM. Combination treatment with STI571 and 5-FU or paclitaxel enhanced the cytotoxic effect somewhat when the concn. of STI571 was increased to 10 μM. Combination treatment with STI571 and 5-FU or paclitaxel enhanced the antitumor effect of the antitumor drug significantly in vivo. The enhanced antitumor effect was assocd. with increased apoptotic cell death and inhibition of tumor angiogenesis. Treatment with STI571 down-regulated the expression of PDGF-BB and PDGFR-β in tumor cells and decreased the prodn. of phosphorylated PDGFR-β and phosphorylated Akt. Furthermore, treatment with STI571 inhibited the expression of PDGFR-β in stromal cells. CONCLUSIONS: STI571 was an effective chemosensitizer of antitumor drugs, such as 5-FU and paclitaxel for gastric carcinoma, targeting the PDGF/PDGFR-signaling pathway of tumor cells and stromal cells in disease progression and angiogenesis.

Answer 31:

Bibliographic Information

CF101, an agonist to the A3 adenosine receptor, enhances the chemotherapeutic effect of 5-fluorouracil in a colon carcinoma murine model. Bar-Yehuda, Sara; Madi, Lea; Silberman, Daniel; Gery, Slosman; Shkapenuk, Maya; Fishman, Pnina. Can-Fite BioPharma Ltd., Petach-Tikva, Israel. Neoplasia (Ann Arbor, MI, United States) (2005), 7(1), 85-90. Publisher: Neoplasia Press Inc., CODEN: NEOPFL ISSN: 1522-8002. Journal written in English. CAN 142:385347 AN 2005:225439 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

NF-κB and the upstream kinase PKB/Akt are highly expressed in chemoresistance tumor cells and may hamper the apoptotic pathway. CF101, a specific agonist to the A3 adenosine receptor, inhibits the development of colon carcinoma growth in cell cultures and xenograft murine models. Because CF101 has been shown to downregulate PKB/Akt and NF-κB protein expression level, we presumed that its combination with chemotherapy will enhance the antitumor effect of the cytotoxic drug. In this study, we utilized 3-[4,5-Dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide (MTT) and colony formation assays and a colon carcinoma xenograft model. It has been shown that a combined treatment of CF101 and 5-fluorouracil (5-FU) enhanced the cytotoxic effect of the latter on HCT-116 human colon carcinoma growth. Downregulation of PKB/Akt, NF-κB, and cyclin D1, and upregulation of caspase-3 protein expression level were obsd. in cells and tumor lesions on treatment with a combination of CF101 and 5-FU. Moreover, in mice treated with the combined therapy, myelotoxicity was prevented as was evidenced by normal white blood cell and neutrophil counts. These results show that CF101 potentiates the cytotoxic effect of 5-FU, thus preventing drug resistance. The myeloprotective effect of CF101 suggests its development as an add-on treatment to 5-FU.

Answer 32:

Bibliographic Information

Gene therapy for colon cancer by adeno-associated viral vector-mediated transfer of survivin Cys84Ala mutant. Tu, Shui Ping; Cui, Jian Tao; Liston, Peter; Jiang, Xiao Hua; Xu, Ruian; Lin, Marie C. M.; Zhu, Yan Bo; Zou, Bing; Ng, Samuel S. M.; Jiang, Shi Hu; Xia, Harry H. X.; Wong, Wai Man; Chan, Annie O. O.; Yuen, Man Fung; Lam, Shiu Kum; Kung, Hsiang Fu; Wong, Benjamin C. Y. Department of Gastroenterology, Rui-jin Hospital, Shanghai, Peop. Rep. China. Gastroenterology (2005), 128(2), 361-375. Publisher: Elsevier Inc., CODEN: GASTAB ISSN: 0016-5085. Journal written in English. CAN 142:366981 AN 2005:203529 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background & Aims: Reactivation of survivin expression is involved in carcinogenesis and angiogenesis in colon cancer. Previous in vitro studies showed that mutation of the cysteine residue at position 84 (Cys84Ala) of survivin generates a dominant-neg. mutant that triggers mitotic catastrophe and apoptosis. We investigated the therapeutic effect of the adeno-assocd. virus (AAV)-mediated survivin mutant (Cys84Ala) on colon cancer. Methods: Survivin mutant (Cys84Ala) (Sur-Mut(Cys84Ala)) was cloned into the AAV expression vector pAM/CAG-WPRE.poly(A) to generate recombinant AAV-Sur-Mut(Cys84Ala) virus. Cell proliferation, apoptosis, mitotic catastrophe, and tumor growth were measured in vitro and in vivo. Results: Transduction of colon cancer cells with rAAV-Sur-Mut(Cys84Ala) inhibited cell proliferation and induced apoptosis and mitotic catastrophe in vitro. RAAV-Sur-Mut(Cys84Ala) sensitized colon cancer cells to chemotherapeutic drugs. Furthermore, expression of survivin mutant mediated by AAV inhibited tumorigenesis in colon cancer cells. Intratumoral injection of rAAV-Sur-Mut(Cys84Ala) significantly induced apoptosis and mitotic catastrophe and inhibited angiogenesis and tumor growth in a colon cancer xenograft model in vivo. No obvious cytotoxicity to other tissues was obsd. More importantly, rAAV-Sur-Mut(Cys84Ala) expression strongly enhanced the antitumor activity of 5-Fluorouracil (5-FU), resulting in regression of established tumors. Conclusions: Our results showed that rAAV-Sur-Mut(Cys84Ala) induced apoptosis and mitotic catastrophe and inhibited tumor angiogenesis and tumor growth. Thus, use of AAV-mediated survivin mutant (Cys84Ala) is a promising strategy in colon cancer gene therapy.

Answer 33:

Bibliographic Information

Synergistic antitumor activity of capecitabine in combination with irinotecan. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Colorectal Cancer (2005), 4(5), 336-343. Publisher: Cancer Information Group, CODEN: CCCLCF ISSN: 1533-0028. Journal written in English. CAN 142:385338 AN 2005:198981 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (5-FU) and capecitabine alone and in combination with irinotecan/oxaliplatin are clin. active in the treatment of colorectal and other solid tumors. Studies of the antitumor activity and toxicity of capecitabine or irinotecan alone and in combination with each other, were compared with 5-FU and raltitrexed in human tumor xenografts of colorectal and squamous cell carcinoma of the head and neck using clin. relevant schedules. Antitumor activity and toxicity were evaluated in nude mice bearing human colon carcinomas of HCT-8 and HT-29 and in head and neck squamous cell carcinomas of A253 and FaDu xenografts using the max. tolerable dose of single-agent capecitabine, 5-FU, or raltitrexed, or each of the drugs in combination with irinotecan. Mice were treated with capecitabine and irinotecan alone or in combination using 2 different schedules: (1) capecitabine orally once a day for 7 days and a single dose of irinotecan (50 mg/kg i.v.), with each drug alone or in combination, and (2) capecitabine orally 5 days a week for 3 wk and irinotecan 50 mg/kg (I.V. injection) once a week for 3 wk, with each drug alone or in combination. For comparative purposes, the antitumor activity of single-agent capecitabine, 5-FU, or raltitrexed, or each drug in combination with irinotecan was carried out at its max. tolerated dose (MTD) using a 3-wk schedule. Results indicated that HT-29 and A253 xenografts were de novo resistant (no cure) to capecitabine and irinotecan alone at the MTD, whereas HCT-8 and FaDu xenografts were relatively more sensitive, yielding 10-20% cures. The combination of irinotecan/capecitabine was much more active than either drug alone against all 4 tumor models. The cure rates were increased from 0 to 20% in A253 and HT-29 xenografts and from 10-20% to 80-100% in HCT-8 and FaDu tumor xenografts, resp. Irinotecan/capecitabine had clear advantage over irinotecan/5-FU and irinotecan/raltitrexed in efficacy and selectivity in that they were more active and less toxic.

The extent of synergy with irinotecan/capecitabine appears to be tumor-dependent and independent of the status of p53 expression. The potential impact of the preclin. results on clin. practice for the use of these drugs in combination needs clin. validation.

Answer 34:

Bibliographic Information

Antitumour activity of XR5944 in vitro and in vivo in combination with 5-fluorouracil and irinotecan in colon cancer cell lines. Harris, S. M.; Mistry, P.; Freathy, C.; Brown, J. L.; Charlton, P. A. Xenova Ltd, Berkshire, UK. British Journal of Cancer (2005), 92(4), 722-728. Publisher: Nature Publishing Group, CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 142:456397 AN 2005:151667 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

XR5944 (MLN944), a novel bis-phenazine, has demonstrated potent cytotoxic activity against a variety of murine and human tumor models. In the present study, the antitumor activity of XR5944 was investigated in combination with 5-fluorouracil (5-FU) or irinotecan in human colon carcinoma cell lines and xenografts. In vitro cytotoxicity of the combinations following exposure to the drugs sequentially or simultaneously was evaluated by the sulforhodamine-B assay and interactions were detd. using median-effect anal. Antagonism was obsd. (CI>1) following exposure of HT29 cells simultaneously to XR5944 and 5-FU or SN38 (active metabolite of irinotecan). In contrast, sequential exposure of either combination in either order demonstrated at least an additive response (CI $\leq$ 1). At least an additive response was also obsd. with these combinations in HCT116 cells regardless of schedule. Antitumor activity in HT29 xenografts in nude mice was enhanced by sequential administration of 5-FU (65 mg kg-1) or irinotecan (CPT-11) (35 mg kg-1) 48 h before XR5944 (5, 10, or 15 mg kg-1) compared to single agent treatment at the same or higher doses. Administration of irinotecan (35 mg kg-1) and XR5944 (15 mg kg-1) just 30 min apart yielded similar efficacy to sequential administration 48 h apart. All combinations were well tolerated. These data suggest that combinations of XR5944 with irinotecan or 5-FU are of significant interest in the treatment of colon cancer.

Answer 35:

Bibliographic Information

Tumor-specific intravenous gene delivery using oncolytic adenoviruses. Zhan, Jinghui; Gao, Yi; Wang, Wensheng; Shen, Annie; Aspelund, Amy; Young, Mandy; Laquerre, Sylvie; Post, Leonard; Shen, Yuqiao. Onyx Pharmaceuticals Inc., Richmond, CA, USA. Cancer Gene Therapy (2005), 12(1), 19-25. Publisher: Nature Publishing Group, CODEN: CGTHEG ISSN: 0929-1903. Journal written in English. CAN 142:170652 AN 2004:1072492 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In this report, we describe a vector system that specifically delivers transgene products to tumors following i.v. administration. The Escherichia coli cytosine deaminase (CD) gene was placed in the E3B region of the tumor-selective, replication-competent adenovirus ONYX-411, under the control of endogenous viral late gene regulatory elements. Thus, CD expression was directly coupled to the tumor-selective replication of the viral vector. In vitro, CD was expressed efficiently in various human cancer cell lines tested but not in cultured normal human cells, including human hepatocytes. Following i.v. administration into nude mice carrying human tumor xenografts, robust CD activity was detected only in tumors but not in liver or other normal tissues. Levels of CD activity in the tumors increased progressively following i.v. virus administration, correlating closely with virus replication in vivo. Subsequent administration of 5-fluorocytosine (5-FC) demonstrated a trend to improve the antitumor efficacy of these viruses in a mouse xenograft model, presumably due to the intratumoral conversion of 5-FC to the chemotherapeutic drug 5-fluorouracil. We show that the combination of a highly selective oncolytic virus, ONYX-411, with the strategic use of the viral E3B region for transgene insertion provides a powerful platform that allows for tumor-specific, persistent and robust transgene expression after i.v. administration. This technol. provides an opportunity to enhance greatly the efficacy of cancer gene therapy.

Answer 36:

Bibliographic Information

Preclinical evaluation of antisense bcl-2 as a chemosensitizer for patients with gastric carcinoma. Kim, Ryungsa; Emi, Manabu; Tanabe, Kazuaki; Toge, Tetsuya. Department of Surgical Oncology, Research Institute for Radiation Biology and Medicine, Hiroshima University, Hiroshima, Japan. Cancer (New York, NY, United States) (2004), 101(10), 2177-2186. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 142:253981 AN 2004:1061374 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND: Because bcl-2 is a crit. factor for anticancer drug-induced apoptosis, the authors conducted a preclin. evaluation of antisense (AS) bcl-2 as an enhancer of the chemotherapeutic effect in the treatment of patients with gastric carcinoma. METHODS: AS bcl-2 was used with 18-mer phosphorothiated oligonucleotides in the MKN-45 gastric carcinoma cell line. Drug sensitivity in vitro was evaluated using the methyl-thiazoldiphenyl tetrazolium assay, and antitumor effects in vivo were evaluated using the nude mouse xenograft. Apoptosis was detd. with the terminal deoxyuridine triphosphate nick-end labeling assay. AS bcl-2 in vitro was treated with lipofectin, whereas it was administered i.p. for 6 consecutive days twice every 2 wk in vivo. Anticancer drugs were administered i.p. four times per wk. RESULTS: bcl-2 was down-regulated to 60% of its initial value after treatment with 1.0 μM AS bcl-2 compared with the controls of random and mismatched oligonucleotides. Drug sensitivity to doxorubicin, cisplatin, and paclitaxel (TXL) was increased 3-4-fold when used in combination with AS bcl-2, which was detd. with 50% inhibitory concn. values, compared with the control group. Increased drug sensitivity was assocd. with apoptosis, which increased in Bax and poly-ADP (ADP-ribose) polymerase and decreased in phosphorylated Akt (pAkt). The antitumor effect of cisplatin and TXL in vivo was enhanced significantly in combination with AS bcl-2. Down-regulation of bcl-2 was obsd. on Day 4 after the treatment with AS bcl-2. CONCLUSIONS: Combination treatment with AS bcl-2 and anticancer drugs, including cisplatin and TXL, may be a new strategy for enhancing chemotherapeutic effects in the treatment of gastric carcinoma.

Answer 37:

Bibliographic Information

Investigations in vivo of the effects of carbogen breathing on 5-fluorouracil pharmacokinetics and physiology of solid rodent tumours. McSheehy, P. M. J.; Port, R. E.; Rodrigues, L. M.; Robinson, S. P.; Stubbs, M.; Borns, K.; Peters, G. J.; Judson, I. R.; Leach, M. O.; Griffiths, J. R. Department of Biochemistry, Cancer Research UK Biomedical Magnetic Resonance Research Group, St George's Hospital Medical School, London, UK. Cancer Chemotherapy and Pharmacology (2005), 55(2), 117-128. Publisher: Springer GmbH, CODEN: CCPHDZ ISSN: 0344-5704. Journal written in English. CAN 142:309302 AN 2004:1053640 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Purpose: We have shown previously that carbogen (95 02, 5 CO2) breathing by rodents can increase uptake of anticancer drugs into tumors. The aim of this study was to extend these observations to other rodent models using the anticancer drug 5-fluorouracil (5FU). 5FU pharmacokinetics in tumor and plasma and physiol. effects on the tumor by carbogen were investigated to det. the locus of carbogen action on augmenting tumor uptake of 5FU. Methods: Two different tumor models were used, rat GH3 prolactinomas xenografted s.c. into nude mice and rat H9618a hepatomas grown s.c. in syngeneic Buffalo rats. Uptake and metab. of 5FU in both tumor models with or without host carbogen breathing was studied non-invasively using fluorine-19 magnetic resonance spectroscopy (19F-MRS), while plasma samples from Buffalo rats were used to construct a NONMEM pharmacokinetic model. Physiol. effects of carbogen on tumors were studied using 31P-MRS for energy status (NTP/Pi) and pH, and gradient-recalled echo magnetic resonance imaging (GRE-MRI) for blood flow and oxygenation. Results: In both tumor models, carbogan-induced GRE-MRI signal intensity increases of .apprx.60 consistent with an increase in tumor blood oxygenation and/or flow. In GH3 xenografts, 19F-MRS showed that carbogen had no significant effect on 5FU uptake and metab. by the tumors, and 31P-MRS showed there was no change in the NTP/Pi ratio. In H9618a hepatomas, 19F-MRS showed that carbogen had no effect on tumor 5FU uptake but significantly ($p=0.0003$) increased 5FU elimination from the tumor (i.e. decreased the t1/2) and significantly ($p=0.029$) increased (53) the rate of metab. to cytotoxic fluoronucleotides (FNuct). The pharmacokinetic anal. showed that carbogen increased the rate of tumor uptake of 5FU from the plasma but also increased the rate of removal. 31P-MRS showed there were significant ($p \leq 0.02$) increases in the hepatoma NTP/Pi ratio of 49 and transmembrane pH gradient of 0.11 units.

Conclusions: We suggest that carbogen can transiently increase tumor blood flow, but this effect alone may not increase uptake of anticancer drugs without a secondary mechanism operating. In the case of the hepatoma, the increase in tumor energy status and pH gradient may be sufficient to augment 5FU metab. to cytotoxic FNuct, while in the GH3 xenografts this was not the case. Thus carbogen breathing does not universally lead to increased uptake of anticancer drugs.

Answer 38:

Bibliographic Information

Lack of microvessels in well-differentiated regions of human head and neck squamous cell carcinoma A253 associated with functional magnetic resonance imaging detectable hypoxia, limited drug delivery, and resistance to irinotecan therapy.
Bhattacharya, Arup; Toth, Karoly; Mazurchuk, Richard; Spernyak, Joseph A.; Slocum, Harry K.; Pendyala, Lakshmi; Azrak, Rami; Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Cancer Biology, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2004), 10(23), 8005-8017. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 142:273563 AN 2004:1048146 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combination chemotherapy with irinotecan (CPT-11; 50 mg/kg/wk x 4 i.v.), followed 24 h later by 5-fluorouracil (50 mg/kg/wk x 4 i.v.), results in 10 and 100% cure rates of animals bearing human head and neck squamous cell carcinoma xenografts A253 and FaDu, resp. A253 consists of 30% well-differentiated and avascular and 70% poorly differentiated regions with low microvessel d. (10/x400), whereas FaDu is uniformly poorly differentiated with higher microvessel d. (19/x400). Studies were carried out for detg. the role of well-differentiated and avascular regions in drug resistance in A253 and detection of such regions with noninvasive functional magnetic resonance (fMR) imaging. Tumors were harvested for histopathol. evaluation and immunohistochem. (CD31, CD34; differentiation marker: involucrin; hypoxia markers: carbonic anhydrase IX, pimonidazole; vascular endothelial factor (VEGF) and Ki67) immediately after fMR imaging following the 3rd dose of chemotherapy. High-performance liq. chromatog. detn. of intratumoral drug concn. of 7-ethyl-10-hydroxyl-camptothecin and autoradiog. with 14C-labeled CPT-11 was done 2 h after CPT-11 administration. Although A253 xenografts showed three times higher concn. of 7-ethyl-10-hydroxyl-camptothecin, FaDu was more responsive to therapy. After therapy, A253 tumor consisted mostly (.apprx.80%) of well-differentiated regions (pos. for involucrin) lacking microvessels with a hypoxic rim (pos. for carbonic anhydrase IX and pimonidazole) contg. few proliferating (Ki67 pos.) poorly differentiated cells. Autoradiog. revealed that well-differentiated A253 tumor regions showed 5-fold lower 14C-labeled CPT-11 concns. compared with poorly differentiated areas ($P < 0.001$). Blood oxygen level dependant fMR imaging was able to noninvasively distinguish the hypoxic and well-vascularized regions within the tumors.

Avascular-differentiated regions in squamous cell carcinoma offer sanctuary to some hypoxic but viable tumor cells (carbonic anhydrase IX and Ki67 pos.) that escape therapy because of limited drug delivery. This study provides direct evidence that because of a specific histol. structure, avascular, well-differentiated hypoxic regions in tumors exhibit low drug uptake and represent a unique form of drug resistance.

Answer 39:

Bibliographic Information

Influence on 5-fluorouracil metabolism by combination of interferon-α and 5-fluorouracil against human hepatocellular carcinoma xenografts. Jin, Chang De; Yamamoto, Tameyoshi; Nakamura, Masato; Arai, Isao; Kishin, Rho; Xing, Xu; Nagano, Hiroaki; Dono, Keizo; Umeshita, Koji; Nakamori, Shoji; Sakon, Masato; Monden, Morito. Dept. of Surgery and Clinical Oncology, Graduate School of Medicine, Osaka University, Japan. Gan to Kagaku Ryoho (2004), 31(10), 1511-1515. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 142:211709 AN 2004:1002930 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To investigate the effect of biochem. modulation on antitumor activity shown by the combination of 5-Fluorouracil (5-FU) and interferon-α (IFN-α), exptl. therapy was performed on human hepatocellular carcinoma cell (HuH7, PLC/PLF/5) xenografts inoculated into nude mice, using 5-FU and IFN-α, either alone or in combination. These agents showed antitumor activity in different degrees. Although IFN-α, given as 100,000 units/mouse/3 times/wk s.c. ×6, and 5-FU, given as 0.5 mg/mouse/3 times/wk i.p., showed additive antitumor effect against HuH7 and PLC/PLF/5, the activities of thymidylate synthase (TS), dihydropyrimidine dehydrogenase (DPD), thymidine phosphorylase (TP), orotate phosphoribosyltransferase (OPRT), uridine phosphorylase (UP) and uridine kinase (UK) were not significantly influenced in the tumors treated with the 5-FU/IFN-α combination, compared with those treated with 5-FU or IFN-α alone. This suggested that antitumor activity of 5-FU and IFN-α in combination was not significantly involved in 5-FU metab. in two human hepatocellular carcinoma cell lines examd.

Answer 40:

Bibliographic Information

Inducible Silencing of KILLER/DR5 In vivo Promotes Bioluminescent Colon Tumor Xenograft Growth and Confers Resistance to Chemotherapeutic Agent 5-Fluorouracil. Wang, Shulin; El-Deiry, Wafik S. Departments of Medicine, Genetics, and Pharmacology, and Abramson Cancer Center, University of Pennsylvania School of Medicine, Philadelphia, PA, USA. Cancer Research (2004), 64(18), 6666-6672. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 141:271171 AN 2004:757698 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The candidate tumor suppressor KILLER/DR5 is a DNA damage-inducible p53-regulated death receptor for the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), a promising agent for cancer therapy. The majority of studies on KILLER/DR5 have been focused on its role in TRAIL-induced apoptosis. However, its contribution to the inhibition of tumor growth and its role as a determinant of chemosensitivity are poorly understood. In the present study, the authors have generated stable human colon cancer cell lines, in which the function of KILLER/DR5 was ablated using inducible RNA interference. Inducible silencing of KILLER/DR5 in vivo by exposure of mice to doxycycline led to accelerated growth of bioluminescent tumor xenografts and conferred resistance to the chemotherapeutic agent 5-fluorouracil. Our results suggest that KILLER/DR5 may be a crit. determinant for tumorigenicity and chemosensitivity.

Answer 41:

Bibliographic Information

Changes in thymidylate synthase and its inhibition rate and changes in dihydropyrimidine dehydrogenase after the administration of 5-fluorouracil with cisplatin to nude mice with gastric cancer xenograft SC-1-NU. Sakurai, Yoichi; Uraguchi, Takashi; Imazu, Hiroki; Hasegawa, Shigeru; Matsubara, Toshiki; Ochiai, Masahiro; Funabiki, Takahiko. Department of Surgery, Fujita Health University School of Medicine, Toyoake, Aichi, Japan. Gastric Cancer (2004), 7(2), 110-116. Publisher: Springer-Verlag Tokyo, CODEN: GCANFO ISSN: 1436-3291. Journal written in English. CAN 142:106640 AN 2004:525683 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although 5-fluorouracil (5-FU) and cis-diamminedichloroplatinum (cisplatin) in combination have synergistic cytotoxicity against both murine and human neoplasms, the precise mechanism of the synergism, and the effects on thymidylate synthase (TS) and its percent inhibition, and the effects on dihydropyrimidine dehydrogenase (DPD) remained to be elucidated. Exptl. chemotherapy was performed using SC-1-NU, a human gastric carcinoma xenograft. SC-1-NU was maintained by serial transplantation in male BALB/c nude mice. The nude mice received various chemotherapeutic regimens consisting of 5-FU and/or cisplatin, with different dosages and periods of administration. After the treatment, we examd. the in vivo effects of 5-FU and cisplatin in each regimen on thymidylate synthase and its percent inhibition, and the effects on DPD, in addn. to the observation of tumor growth inhibition. The combined use of 5-FU (20 mg/kg per day) and cisplatin (either 1.5 or 7.5 mg/kg per day) showed a synergistic antitumor effect, regardless of the different doses of cisplatin. The long-term administration of 5-FU significantly increased both total thymidylate synthase and the percent thymidylate synthase inhibition rate. The short-term administration of 5-FU significantly decreased DPD. Nevertheless, these changes showed no relation to the combined use of cisplatin. Combined administration of cisplatin with 5-FU did not further increase thymidylate synthase inhibition over that occurring with 5-FU alone, which does not support the hypothesis that cisplatin combined with 5-FU modulates thymidylate synthase inhibition in enhancing the anticancer effect of 5-FU. Changes in DPD after the administration of 5-FU may provide an insight into tumor sensitivity and resistance to 5-FU.

Answer 42:

Bibliographic Information

Pharmacokinetics, safety, and efficacy of a liposome encapsulated thymidylate synthase inhibitor, OSI-7904L [(S)-2-[5-[(1,2-Dihydro-3-methyl-1-oxobenzo[f]quinazolin-9-yl)methyl]amino-1-oxo-2-isoindolynl]glutaric acid] in mice. Desjardins, John; Emerson, David L.; Colagiovanni, Dorothy B.; Abbott, Elizabeth; Brown, Eric N.; Drolet, Daniel W. OSI Pharmaceuticals, Inc., Boulder, CO, USA. Journal of Pharmacology and Experimental Therapeutics (2004), 309(3), 894-902. Publisher: American Society for Pharmacology and Experimental Therapeutics, CODEN: JPETAB ISSN: 0022-3565. Journal written in English. CAN 141:16844 AN 2004:454430 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

OSI-7904L is a liposomal formulation of the highly specific, noncompetitive, thymidylate synthase inhibitor OSI-7904 (also known as GW1843, 1843U89, and GS7904). The liposome formulation was developed to enhance the therapeutic index and dose schedule convenience of this potent antifolate compd. The studies presented here were conducted to det. the antitumor efficacy, distribution, pharmacokinetics, and safety of OSI-7904L in mice. In a human colon adenocarcinoma xenograft model in mice, OSI-7904L demonstrated superior antitumor efficacy compared with OSI-7904 or 5-fluorouracil. Furthermore, OSI-7904L could be administered less frequently than OSI-7904 although still generating greater tumor growth inhibition. Distribution studies confirmed that OSI-7904L-treated animals had much greater plasma, tissue, and tumor exposure than did OSI-7904-treated animals. Tumor exposures, based on area under the curve, in OSI-7904L-treated mice were increased over 100-fold compared with tumor exposures in OSI-7904-treated mice. Plasma exposures following OSI-7904L administration were greater than dose proportional consistent with satn. of plasma clearance mechanisms. OSI-7904L was much more toxic than OSI-7904 in the mouse with primary toxicities to the intestines, bone marrow, and thymus. Minimal toxicity to the lungs and liver was noted. These data clearly demonstrated that in mice, OSI-7904L has an increased plasma residence time as well as increased tissue and tumor exposure compared with OSI-7904, thus resulting in increased potency and toxicity. Potential benefits of OSI-7904L include improved efficacy and a more convenient schedule of administration.

Answer 43:

Bibliographic Information

Noninvasive measurements of capecitabine metabolism in bladder tumors overexpressing thymidine phosphorylase by fluorine-19 magnetic resonance spectroscopy. Chung, Yuen-Li; Troy, Helen; Judson, Ian R.; Leek, Russell; Leach, Martin O.; Stubbs, Marion; Harris, Adrian L.; Griffiths, John R. Department of Basic Medical Sciences, Cancer Research United Kingdom Biomedical Magnetic Resonance Group, St. George's Hospital Medical School, London, UK. Clinical Cancer Research (2004), 10(11), 3863-3870. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:420011 AN 2004:446458 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Previous studies have shown that tumor response to capecitabine strongly correlates with tumor thymidine phosphorylase (TP). The aims of our study were to (a) investigate the pharmacol. role of TP by measuring the pharmacokinetics (PK) of capecitabine in a human bladder tumor model that was characterized by the overexpression of TP and (b) develop the use of PK measurements for capecitabine by fluorine-19 magnetic resonance spectroscopy as a noninvasive surrogate marker for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients. TP overexpressing (2T10) and control tumors were grown s.c. in nude mice. Mice were given a dose of capecitabine or 5'-deoxy-5-fluorouridine (5'DFUR). 19F tumor spectra were acquired for detn. of rate consts. of capecitabine breakdown and buildup and subsequent breakdown of intermediates, 5'-deoxy-5-fluorocytidine (5'DFCR) and 5'DFUR. The rate const. of 5'DFUR breakdown was also evaluated. The rate const. of breakdown of intermediates was significantly faster in 2T10 tumors than controls ($P < 0.003$). No significant differences in the rate of capecitabine breakdown or intermediate buildup were obsd. The rate const. of 5'DFUR breakdown in the 2T10 tumors was doubled compared with controls ($P < 0.001$). This study confirmed the expected pathway of capecitabine metab. and showed that the level of TP was related to the rate of 5'DFUR conversion. Using in vivo fluorine-19 magnetic resonance spectroscopy to measure the PK of capecitabine and its intermediate metabolites in tumors may provide a noninvasive surrogate method for detg. TP levels in tumors and for predicting tumor response to capecitabine in patients.

Answer 44:

Bibliographic Information

Selective modulation of the therapeutic efficacy of anticancer drugs by selenium containing compounds against human tumor xenografts. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2004), 10(7), 2561-2569. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:360262 AN 2004:290939 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Studies were carried out in athymic nude mice bearing human squamous cell carcinoma of the head and neck (FaDu and A253) and colon carcinoma (HCT-8 and HT-29) xenografts to evaluate the potential role of selenium-contg. compds. as selective modulators of the toxicity and antitumor activity of selected anticancer drugs with particular emphasis on irinotecan, a topoisomerase I poison. Antitumor activity and toxicity were evaluated using nontoxic doses (0.2 mg/mouse/day) and schedule (14-28 days) of the selenium-contg. compds., 5-methylselenocysteine and seleno-L-methionine, administered orally to nude mice daily for 7 days before i.v. administration of anticancer drugs, with continued selenium treatment for 7-21 days, depending on anticancer drugs under evaluation. Several doses of anticancer drugs were used, including the max. tolerated dose (MTD) and toxic doses. Although many chemotherapeutic agents were evaluated for toxicity protection by selenium, data on antitumor activity were primarily obtained using the MTD, 2 x MTD, and 3 x MTD of weekly x4 schedule of irinotecan. Selenium was highly protective against toxicity induced by a variety of chemotherapeutic agents. Furthermore, selenium increased significantly the cure rate of xenografts bearing human tumors that are sensitive (HCT-8 and FaDu) and resistant (HT-29 and A253) to irinotecan. The high cure rate (100%) was achieved in nude mice bearing HCT-8 and FaDu xenografts treated with the MTD of irinotecan (100 mg/kg/wk x 4) when combined with selenium. Administration of higher doses of irinotecan (200 and 300 mg/kg/wk x 4) was required to achieve high cure rate for HT-29 and A253 xenografts. Administration of these higher doses was possible due to selective protection of normal tissues by selenium. Thus, the

use of selenium as selective modulator of the therapeutic efficacy of anticancer drugs is new and novel.
We demonstrated that selenium is a highly effective modulator of the therapeutic efficacy and selectivity of anticancer drugs in nude mice bearing human tumor xenografts of colon carcinoma and squamous cell carcinoma of the head and neck. The obsd. in vivo synergic interaction is highly dependent on the schedule of selenium.

Answer 45:

Bibliographic Information

Clonogenic assay with established human tumour xenografts: correlation of in vitro to in vivo activity as a basis for anticancer drug discovery. Fiebig, H. H.; Maier, A.; Burger, A. M. Oncotest GmbH, Institute for Experimental Oncology, Freiburg, Germany. European Journal of Cancer (2004), 40(6), 802-820. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:342988 AN 2004:284718 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pluripotent cells can be grown in clonogenic assays. The tumor stem-cell fraction, which accounts for <0.4% of the total cells, and which is considered the most relevant cell type in the development of metastases and recurrences, is able to divide and to form colonies in a semisolid matrix (agar or methylcellulose). Major applications of the tumor clonogenic assay (TCA) are chemosensitivity testing of tumors and xenografts, and for assessments within drug discovery programs. Of crit. relevance for the usefulness of the TCA is whether it can predict sensitivity or resistance towards clin. used agents. When we compared the response of human tumors established as xenografts in nude mice in the TCA in vitro to that of the clin. response, 62% of the comparisons for drug sensitivity, and 92% of the comparisons for drug resistance were correct. The same percentage of true/false observations was found when tumors were tested after serial passage in nude mice in the TCA in vitro and their response compared to in vivo activity in corresponding xenografts (60% and 90%, resp.). The highest correct predictive values were, however, found when the clin. response of tumors was compared to their explants established in the nude mouse and treated in vivo. Of 80 comparisons performed, we obsd. a correct prediction for tumor resistance in 97% and for tumor sensitivity in 90%. In our opinion, the TCA with established human tumor xenografts has an important role in current drug discovery strategies. We therefore included the TCA as secondary assay in our approach to anticancer drug discovery and found that a no. of novel agents were active; these are now in advanced preclin. development or clin. trials. Thus, the tumor clonogenic assay has proven predictive value in the chemosensitivity testing of std. and exptl. anticancer drugs.

Answer 46:

Bibliographic Information

Combined 5-fluorouracil/systemic interferon-β gene therapy results in long-term survival in mice with established colorectal liver metastases. Choi, Eugene A.; Lei, Hanqin; Maron, David J.; Mick, Rosemarie; Barsoum, James; Yu, Qian-chun; Fraker, Douglas L.; Wilson, James M.; Spitz, Francis R. Department of Surgery, Division of Surgical Oncology, The University of Pennsylvania Medical Center, Philadelphia, PA, USA. Clinical Cancer Research (2004), 10(4), 1535-1544. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:235817 AN 2004:145058 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Preclin. in vitro and in vivo studies have demonstrated synergistic interactions between 5-fluorouracil (5-FU) and type I and II IFNs against human colorectal cancer cells. Despite these activities, randomized human trials have failed to identify a clin. benefit for this combination treatment. These limited clin. results may be secondary to the short half-life of recombinant IFN protein and the increased systemic toxicities of 5-FU/IFN combinations. We have previously reported an adenoviral-mediated IFN-β gene therapy strategy, which may circumvent the pitfalls of recombinant IFN therapy. However, a dose-dependent toxicity and acute inflammatory response to systemically administered adenovirus vectors may limit the clin. application of this therapy. The combination of

adenoviral-mediated IFN-β gene therapy and 5-FU resulted in tumor regression, apoptosis, and improved survival in an established liver metastases model. These therapeutic effects were obsd. at a significantly lower vector dose than we had previously reported and with limited toxicity. This approach may allow for an effective clin. application of this therapy and warrants addnl. investigation.

Answer 47:

Bibliographic Information

Therapeutic synergy between irinotecan and 5-fluorouracil against human tumor xenografts. Azrak, Rami G.; Cao, Shousong; Slocum, Harry K.; Toth, Karoly; Durrani, Farukh A.; Yin, Ming-biao; Pendyala, Lakshmi; Zhang, Wanghai; McLeod, Howard L.; Rustum, Youcef M. Department of Pharmacology and Therapeutics and Medicine, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2004), 10(3), 1121-1129. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 141:218407 AN 2004:114400 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Although the combination of irinotecan and 5-fluorouracil is clin. active, it is assocd. with significant toxicity and resistance. Studies were carried out to define the optimal dosage, sequence, and timing for the combination in mice bearing xenografted human tumors. The max. tolerated dose of irinotecan and 5-fluorouracil in combination was detd. in nude mice. Therapeutic efficacy against established human colon carcinoma xenografts, HCT-8 and HT-29, and human head and neck squamous cell carcinoma xenografts, FaDu and A253, was detd. using the rugs individually, simultaneously, and in sequence with various intervals in between. Treatments were i.v. weekly x 4. Immunohistochem. and reverse transcription-PCR measurements of relevant drug-metabolizing enzymes, apoptosis-related proteins, cell cycle distribution, cyclin A, and S phase fraction expression were carried out and compared with the therapeutic outcome. The max. tolerated dose of irinotecan resulted in cure rates of 30% or less in all xenografts. No cures were achieved with FUra alone. Concurrent administration of irinotecan and FUra, or of FUra 24 h before irinotecan, resulted in cure rates of <20%, except for FaDu (60%). Administration of irinotecan 24 h before FUra resulted in the highest cure rates, 80% in HCT-8, 0% in HT-29, 100% in FaDu, and 10% in A253. The optimal therapeutic synergy was achieved when irinotecan was administered 24 h before 5-Flurouracil. Sensitivity to this combination was assocd. with poor differentiation status, higher cyclin A index, recruitment of cells into S phase, and induction of Bax expression and apoptosis.

Answer 48:

Bibliographic Information

Anticancer drug response and expression of molecular markers in early-passage xenotransplanted colon carcinomas. Fichtner, I.; Slisow, W.; Gill, J.; Becker, M.; Elbe, B.; Hillebrand, T.; Bibby, M. Max-Delbrueck-Center for Molecular Medicine, Berlin, Germany. European Journal of Cancer (2004), 40(2), 298-307. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 141:150528 AN 2004:34767 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Despite some success in the treatment of colorectal carcinomas, novel rational therapies targeting specific cancer-related mols. are under development and urgently needed. These approaches need careful preclin. evaluation in models that closely mirror the clin. situation. Therefore, we established a panel of 15 xenotransplantable tumors directly from fresh surgical material. We showed that both the histol. and expression of tumor-assocd. markers (Epithelial Cell Adhesion mol. (EpCAM), E-cadherin, carcinoembryonic antigen (CEA)) could be maintained during passaging in nude mice. Xenotransplanted tumors were characterized for chemosensitivity and revealed a response rate of 5/15 (33%) for 5-fluorouracil (5-FU), 15/15 (100%) for irinotecan and 8/14 (57%) for oxaliplatin. 5 Patients out of 15 were treated with cytostatics because of synchronous metastases. The response to chemotherapy in these patients coincided very closely with the response of the individual xenografts. All of the xenografts expressed the proliferation marker Ki67 and the nuclear enzyme, Topoisomerase IIα (Topo IIα) at the protein level. Most of the xenografts also expressed the tumor suppressor, p53 (9/14) and the nuclear enzyme Topoisomerase Iα (Topo Iα) (13/14) at the protein level. Interestingly, the presence of

a K-ras mutation in codon 12 (5/15 xenografts) coincided with a low response rate towards oxaliplatin. This observation needs further confirmation using a larger no. of tumors. In conclusion, we were able to establish transplantable xenografts suitable to mimic the clin. situation. These well characterized models are useful tools for the preclin. development of novel therapeutic approaches and for investigating translational research aspects.

Answer 49:

Bibliographic Information

Metabolism of a novel nucleoside analogue, OGT 719, in the isolated perfused rat liver model, in rats, in tumour models and in patients. Desmoulin, F.; Gilard, V.; Malet-Martino, M.; Martino, R.; Molina, C.; Smith, P. UMR CNRS 5623, Biomedical NMR Group, Universite Paul Sabatier, Toulouse, Fr. Xenobiotica (2003), 33(3), 289-303. Publisher: Taylor & Francis Ltd., CODEN: XENOBH ISSN: 0049-8254. Journal written in English. CAN 139:159397 AN 2003:203790 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The metabolic pathway(s) of OGT 719, a novel nucleoside analog in which galactose is covalently attached to the N1 of 5-fluorouracil (FU), have been investigated with 19F-NMR spectroscopy in (1) the isolated perfused rat liver (IPRL) model, (2) normal rats, (3) rats bearing the HSN LV10 sarcoma, (4) nude mice xenografted with the human hepatoma HepG2 and (5) urine from patients. The administration of OGT 719 results in the formation of small amts. of FU. IPRL expts. with OGT 719 in combination with asialofetuin, a natural asialoglycoprotein receptor (ASGP-r), suggest competitive binding of OGT 719 to the ASGP-r. The data obtained in non-tumor rats also demonstrated an extremely low metabolization of OGT 719 into FU and α-fluoro-β-alanine, the well-known major metabolite of FU. A comparison of tumor exts. from rats bearing the HSN LV10 sarcoma treated with FU or OGT 719 showed the incorporation of FU into RNA in rats treated with FU but not in rats treated with OGT 719; nevertheless, the incorporation of FU into RNA was obsd. in the liver from rats treated with OGT 719. In a human hepatoma xenografted to nude mice, both the OGT 719 and FU contents of the tumor were markedly higher than in the corresponding liver, suggesting a tumor-specific trapping of OGT 719 in hepatoma. The metab. of OGT 719 was also extremely low in patients. In conclusion, the present study shows the value of 19F-NMR for demonstrating for the first time that OGT 719 is a prodrug of FU although very poorly metabolized.

Answer 50:

Bibliographic Information

Genome-wide cDNA microarray screening to correlate gene expression profiles with sensitivity of 85 human cancer xenografts to anticancer drugs. Zembutsu, Hitoshi; Ohnishi, Yasuyuki; Tsunoda, Tatsuhiko; Furukawa, Yoichi; Katagiri, Toyomasa; Ueyama, Yoshito; Tamaoki, Norikazu; Nomura, Tatsuji; Kitahara, Osamu; Yanagawa, Rempei; Hirata, Koichi; Nakamura, Yusuke. Laboratory of Molecular Medicine, Human Genome Center, Institute of Medical Science, The University of Tokyo, Tokyo, Japan. Cancer Research (2002), 62(2), 518-527. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 136:395496 AN 2002:108259 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

One of the most crit. issues to be solved in regard to cancer chemotherapy is the need to establish a method for predicting efficacy or toxicity of anticancer drugs for individual patients. To identify genes that might be assocd. with chemosensitivity, we used a cDNA microarray representing 23,040 genes to analyze expression profiles in a panel of 85 cancer xenografts derived from nine human organs. The xenografts, implanted into nude mice, were examd. for sensitivity to nine anticancer drugs (5-fluorouracil, 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-1-(2-chloroethyl)-1-nitrosourea hydrochloride, adriamycin, cyclophosphamide, cisplatin, mitomycin C, methotrexate, vincristine, and vinblastine). Comparison of the gene expression profiles of the tumors with sensitivities to each drug identified 1,578 genes whose expression levels correlated significantly with chemosensitivity; 333 of those genes showed significant correlation with two or more drugs, and 32 correlated with six or seven drugs. These data should contribute useful

information for identifying predictive markers for drug sensitivity that may eventually provide "personalized chemotherapy" for individual patients, as well as for development of novel drugs to overcome acquired resistance of tumor cells to chem. agents.

Answer 51:

Bibliographic Information

Experimental chemotherapy against canine mammary cancer xenograft in SCID mice and prediction of its clinical effect. Yamashita, Atsuko; Maruo, Kohji; Suzuki, Kaoru; Shirota, Kinji; Kobayashi, Kimio; Hioki, Kyoji. Department of Veterinary Surgery, Tokyo University of Agriculture and Technology, Tokyo, Japan. Journal of Veterinary Medical Science (2001), 63(8), 831-836. Publisher: Japanese Society of Veterinary Science, CODEN: JVMSEQ ISSN: 0916-7250. Journal written in English. CAN 136:379575 AN 2001:706827 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effectiveness of 6 antitumor agents was evaluated for a canine mammary gland tumor (CMG-6) serially transplanted into mice with severe combined immunodeficiency. CMG-6, a solid carcinoma, was s.c. transplanted into immunodeficient mice, and 6 antitumor agents were given i.v. as a single injection. The min. EDs (MEDs; mg/kg) in mice were: cyclophosphamide (CPM) 65, doxorubicin (DXR) 6, cisplatin (CDDP) 5, vincristine (VCR) 1.6, vinblastine (VLB) >5.5, 5-fluorouracil (5-FU) 105. The clin. effects of the drugs were predicted based on the ratio of the area under the curve (AUC) in dogs given a clin. dose (AUC dog) to the AUC of mice given a MED (AUC mouse) from published refs. The AUC ratios were: CPM 2.24, DXR 0.19, CDDP 1.20, VCR 0.04, VLB <1.24 and 5-FU 1.15. The drugs having a value of >1.0 for the AUC dog/AUC mouse ratio were CPM, CDDP and 5-FU, suggesting that they might be effective in the original dogs with CMG-6. Combination chemotherapy using clin. equiv. doses of CDDP and CPM, which had the two highest values of the AUC dog/AUC mouse ratio in single-agent therapy, had addnl. effects as compared to the effectiveness of the single agents against CMG-6.

Answer 52:

Bibliographic Information

Thymidylate synthase (TS) and ribonucleotide reductase (RNR) may be involved in acquired resistance to 5-fluorouracil (5-FU) in human cancer xenografts in vivo. Fukushima, M.; Fujioka, A.; Uchida, J.; Nakagawa, F.; Takechi, T. The Second Cancer Laboratory, Taiho Pharmaceutical Co., Ltd., Hanno, Saitama, Japan. European Journal of Cancer (2001), 37(13), 1681-1687. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 136:363331 AN 2001:627979 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human tumor sub-line resistant to 5-fluorouracil (5-FU) was established by once a day and every 5, with at least 50 administrations of 5-FU to KM12C human colorectal xenografts in nude mice. KM12C tumors treated with 5-FU showed less sensitivity to 5-FU with an inhibition rate (IR) of 7.9%, while non-treated tumors were highly sensitive to 5-FU with an IR of 81.8%. To clarify the mechanism of 5-FU-resistance, the activities of various enzymes and gene expressions involved in the metab. of 5-FU in both parental and 5-FU-treated KM12C tumors were measured. A 2- to 3-fold increase in thymidylate synthase (TS) activity and 4- to 5-fold decrease in ribonucleotide reductase (RNR) activity were obsd. in 5-FU-resistant KM12C tumors, while the activities of orotate phosphoribosyltransferase (OPRT) thymidine and uridine phosphorylases (TP,UP) and thymidine kinase (TK) were not markedly changed as a consequence of repeated treatment of KM12C tumors with 5-FU. The expression of TS mRNA was also amplified in accordance with the increased TS activity in a 5-FU-treated tumor sub-line (KM12C/5-FU) compared with that in parental tumors, but changed expressions of both RNR-R1 and RNA-R2 mRNA could not be detected in the 5-FU-resistant tumor sub-line compared with the parental tumors, suggesting possible post-transcriptional regulation of RNR. Moreover, RNR, in addn. to TS and OPRT, seemed to be related to the inherent insensitivity to 5-FU in human cancer xenografts. From these results, it may be concluded that RNR activity is one of the acquired or inherent resistant factors, including TS, to 5-FU in human cancer xenografts in vivo.

Answer 53:

Bibliographic Information

In vivo antitumor efficacy of MGI-114 (6-hydroxymethylacylfulvene, HMAF) in various human tumor xenograft models including several lung and gastric tumors. Sato, Y.; Kashimoto, S.; MacDonald, J. R.; Nakano, K. Discovery Research Laboratories, Department of Pharmacology II, Dainippon Pharmaceutical Co., Ltd., Suita, Osaka, Japan. European Journal of Cancer (2001), 37(11), 1419-1428. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 136:288614 AN 2001:483139 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in vivo antitumor efficacy of MGI-114 (a semisynthetic analog of the cytotoxic sesquiterpenoid illudins) was examd. in a panel of human tumor xenografts in mice, consisting mainly of human lung and gastric tumors, and compared with that of other antitumor drugs (irinotecan, paclitaxel, cisplatin, doxorubicin, vindesine, etoposide and 5-fluorouracil). When different administration schedules were compared, daily administration of MGI-114 was more effective than intermittent administrations. In human tumor xenograft models of nasopharyngeal, breast and colon carcinoma and melanoma, MGI-114 exerted a strong antitumor activity, with complete tumor regression occurring. Moreover, in four human lung and three gastric tumor xenografts, MGI-114 had a strong antitumor activity, with complete tumor regression occurring in some cases. The antitumor efficacy of MGI-114 was generally higher than or equiv. to that of irinotecan and paclitaxel. These results support the potential utility of MGI-114 in the treatment of a variety of human solid tumors.

Answer 54:

Bibliographic Information

Activity of boanmycin against colorectal cancer. Deng, Yong Chuan; Zhen, Yong Su; Zheng, Shu; Xue, Yu Chuan. Cancer Institute, Medical School, Zhejiang University, Hangzhou, Peop. Rep. China. World Journal of Gastroenterology (2001), 7(1), 93-97. Publisher: World Journal of Gastroenterology, CODEN: WJGAF2 ISSN: 1007-9327. Journal written in English. CAN 135:174776 AN 2001:155070 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A study was conducted in which a human colorectal tumor xenograft model in nude mice and the orthotopic model of murine colon cancer was used to clarify the antitumor effect of boanmycinin comparison with that of mitomycin C and 5-fluorouracil, drugs commonly used in clinics against colorectal cancer. The effect of BAM against colorectal cancer was detd. It was also examd. whether the organ microenvironment could influence the response of a murine colon cancer to systemic therapy with BAM. Results demonstrated that, using the orthotopic implantation technique, murine adenocarcinoma CT-26 can successfully produce an aggressive tumor which retained the morphol. biol. characteristics of the donor tumor and metastasized to the mesenteric glands. BAM inhibited tumor growth on CT-26 implanted into the cecum and s.c more than 5-fluorouracil and mitomycin C at the equitoxic dose. Moreover, the inhibitory effect BAM on the growth of CT-26 tumor was higher at the cecum than at the s.c site in mice, which implicates that BAM may have an organ-specific effect.

Answer 55:

Bibliographic Information

Anticancer effects of 5-fluorouracil combined with cisplatin using gastrointestinal cancer xenografts transplanted into nude mice. Uraguchi, Takashi; Sakurai, Yoichi; Nakayama, Kunihisa; Nozoe, Yasutomo; Kobayashi, Hidetaka; Shoji, Mitsutaka; Jinbo, Yasuko; Kanno, Osamu; Uchimura, Masashi; Imazu, Hiroki; Hasagawa, Shigeru; Matsubara, Toshiki. Dept. of Surgery, Fujita Health University School of Medicine, Japan. Fujita Gakuen Igakkaishi (2000), 24(1), 85-89. Publisher: Fujita Gakuen Igakkai, CODEN: FGIGDO ISSN: 0288-5441. Journal written in Japanese. CAN 134:336043 AN 2000:839934 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anticancer effects of 5-fluorouracil combined with cisplatin were better than that of each drug alone, as studied by using gastrointestinal cancer xenografts transplanted into nude mice.

Answer 56:

Bibliographic Information

Direct in vivo observation of 5-fluorouracil release from a prodrug in human tumors heterotransplanted in nude mice: A magnetic resonance study. Guerquin-Kern, Jean-Luc; Volk, Andreas; Chenu, Evelyne; Lougerstay-Madec, Rachel; Monneret, Claude; Florent, Jean-Claude; Carrez, Daniele; Croisy, Alain. Institut Curie Recherche, Laboratoire Raymond Latarjet, INSERM U350, Centre Universitaire, Orsay, Fr. NMR in Biomedicine (2000), 13(5), 306-310. Publisher: John Wiley & Sons Ltd., CODEN: NMRBEF ISSN: 0952-3480. Journal written in English. CAN 134:216762 AN 2000:701197 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A glucuronic acid-conjugated carbamate deriv. of 5-fluorouracil (5-FU), originally designed as a prodrug for antibody-directed enzyme prodrug therapy, was used for direct in vivo observation of in situ 5-FU generation in two human colon tumors heterotransplanted into nude mice. Because of the very fast elimination of glucuronic acid-conjugated drugs, this observation required intratumor injection. These tumors, when becoming necrotic, are rich enough in β-glucuronidase to allow [19F]NMR spectroscopic monitoring, at the tumor level, of both prodrug elimination and 5-FU release without preliminary treatment by a specifically targeted enzyme conjugate. Suitable tumors were selected by NMR imaging on the basis of a correlative study between imaging and conventional histol. This work is the 1st report evidencing such a direct intratumor conversion of a glucuronic acid-conjugated prodrug to the expected active drug. This method, which should allow overall estn. of the β-glucuronidase content of tumors, might also be helpful for selecting tumors as specific targets for nontoxic glucuronic acid-conjugated prodrugs without prior treatment with a fusion protein.

Answer 57:

Bibliographic Information

Effects of ATRA and 5-Fu on growth and telomerase activity of xenografts of gastric cancer in nude mice. Xia, Zhong Sheng; Zhu, Zhao Hua; He, Shou Gao. Department of Gastroenterology, San Yat-Sen Memorial Hospital, Sun Yat-Sen University of Medical Sciences, Canton, Peop. Rep. China. Shijie Huaren Xiaohua Zazhi (2000), 8(6), 674-677. Publisher: Shijie Weichangbingxue Zazhishe, CODEN: SHXZF2 Journal written in Chinese. CAN 133:329224 AN 2000:556999 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

AIM To investigate the influence of ATRA and/or 5-Fu on growth and telomerase activity of xenografts of gastric cancer. METHODS Thirty-four female Balb/c nude mice were randomly divided into control group, solvent control group, ATRA group, 5-Fu group and AF (ATRA plus 5-FU) group. The vols. of xenografts were measured at the 1st and the 11th day of expt. The telomerase activity of xenografts was measured by telomere repeat amplification protocol (TRAP). RESULTS At the 11th day of expt., the vols. of tumors in ATRA group (9.26 mm3 ± 0.84 mm3) and AF group (5.86 mm3 ± 0.87 mm3) were significantly smaller than those in solvent control group (13.41 mm3 ± 3.12 mm3), the vols. of tumors in 5-Fu group (5.92 mm3 ± 1.25 mm3) were significantly smaller than those in control group (13.19 mm3 ± 2.60 mm3). Meanwhile, the telomerase activity of xenografts in ATRA group, 5-Fu group and AF group was 61% (vs. solvent control group, $P<0.01$), 100% and 63% (vs. solvent control group, $P<0.01$). CONCLUSION In vivo, both ATRA and 5-Fu inhibited the growth of s.c. xenografts of gastric cancer in nude mice. ATRA inhibited the telomerase activity of xenografts of gastric cancer, but 5-Fu did not. No synergistic inhibitory effect on the tumor growth and telomerase activity of xenografts of gastric cancer was found when ATRA combined with 5-Fu were given in vivo.

Answer 58:

Bibliographic Information

Epidermal growth factor receptor blockade by antibody IMC-C225 inhibits growth of a human pancreatic carcinoma xenograft in nude mice. Overholser, Jay P.; Prewett, Marie C.; Hooper, Andrea T.; Waksal, Harlan W.; Hicklin, Daniel J. Department of Immunology, ImClone Systems Incorporated, New York, NY, USA. Cancer (New York) (2000), 89(1), 74-82. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 134:99334 AN 2000:516739 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic carcinoma is assocd. with a poor prognosis, and treatment options for patients with this disease are limited. The epidermal growth factor (EGF) receptor and its ligands are overexpressed in human pancreatic carcinoma and may contribute to the pathophysiol. of these tumors. The anti-EGF receptor monoclonal antibody IMC-C225 was used to det. the effects of EGF receptor blockade on the growth of human pancreatic carcinoma BxPC-3 cells in vitro. Athymic mice bearing established (200 mm3) s.c. BxPC-3 xenografts were treated with IMC-C225 (17 or 33 mg/kg every 3 days) alone or in combination with 5-fluorouracil (17 mg/kg twice weekly). IMC-C225 inhibited exogenous ligand-stimulated tyrosine phosphorylation of the EGF receptor on BxPC-3 tumor cells. Treatment of BxPC-3 cells with IMC-C225 inhibited DNA synthesis (23.8%) and colony formation in soft agar (45.6%). IMC-C225 treatment significantly suppressed the growth of BxPC-3 tumors compared with treatment with vehicle alone (P = 0.003). Combination therapy with IMC-C225 and the chemotherapeutic agent 5-fluorouracil enhanced the antitumor effects compared with either agent alone and resulted in regression of pancreatic tumors in several animals. Histol. examn. of pancreatic tumors from mice treated with IMC-C225 showed extensive tumor necrosis that coincided with a substantial decrease in tumor cell proliferation and an increase in tumor cell apoptosis. These data suggest that IMC-C225 affects the growth of pancreatic tumors by inhibiting EGF receptor-dependent proliferation and survival, and demonstrates the potential for therapeutic application of IMC-C225 antibody in the treatment of human pancreatic carcinoma.

Answer 59:

Bibliographic Information

Modulation of 5-fluorouracil host toxicity by 5-(benzyloxybenzyl)barbituric acid acyclonucleoside, a uridine phosphorylase inhibitor, and 2',3',5'-tri-O-acetyluridine, a prodrug of uridine. Ashour, O. M.; Naguib, F. N. M.; Panzica, R. P.; Al Safarjalani, O. N.; el Kouni, M. H. Department of Pharmacology and Toxicology, University of Alabama at Birmingham, Birmingham, AL, USA. Biochemical Pharmacology (2000), 60(3), 427-431. Publisher: Elsevier Science Inc., CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 133:144540 AN 2000:400538 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Administration of 200 mg/kg of 5-fluorouracil (FUra) to mice bearing human colon carcinoma DLD-1 xenografts resulted in 100% mortality. Oral administration of 2000 mg/kg of 2',3',5'-tri-O-acetyluridine (TAU), a prodrug of uridine, in combination with 120 mg/kg of 5-(benzyloxybenzyl)barbituric acid acyclonucleoside (BBBA), the most potent known inhibitor of uridine phosphorylase (UrdPase, EC 2.4.2.3), 2 h after the administration of the same dose of FUra completely protected the mice (100% survival) from the toxicity of FUra. This combination also reduced tumor wt. by 67% compared with 46% achieved by the max. tolerated dose (50 mg/kg) of FUra alone. Similarly, administration of BBBA plus TAU 1 h before or 4 h after the administration of FUra reduced the tumor wt. by 53 and 37%, resp. However, these schedules were less effective in protecting the host from the toxicity of FUra than when the treatment was carried out at 2 h after FUra administration. TAU alone did not protect from FUra host toxicity. The efficiency of the BBBA plus TAU combination in rescuing from FUra host toxicities is attributed to the exceptional effectiveness of this combination in raising and maintaining higher plasma uridine concns. than those achieved by TAU alone or by equimolar doses of uridine (Ashour et al., Biochem. Pharmacol 51: 1601-1612, 1996). The present results suggest that the BBBA plus TAU combination can provide a better substitute for the massive doses of uridine required to achieve the high levels of uridine necessary to rescue or protect from FUra host toxicities without the toxic side-effects assocd. with such doses of uridine. The combination of TAU plus BBBA may also allow the escalation of FUra doses for better chemotherapeutic efficacy. Alternatively, the combination may be used as a rescue regimen in the occasional cases where cancer patients receive a lethal overdose of FUra.

Answer 60:

Bibliographic Information

Treatment regimens including the multitargeted antifolate LY231514 in human tumor xenografts. Teicher, Beverly A.; Chen, Victor; Shih, Chuan; Menon, Krishna; Forler, Patrick A.; Phares, Val G.; Amsrud, Tracy. Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN, USA. Clinical Cancer Research (2000), 6(3), 1016-1023. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 133:114685 AN 2000:242990 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The scheduling of antifolate antitumor agents, including the new multitargeted antifolate LY231514 (MTA), with 5-fluorouracil was explored in the human MX-1 breast carcinoma and human H460 and Calu-6 non-small-cell lung carcinoma xenografts in nude mice to assess antitumor activity and toxicity (body wt. loss). Administration of an antifolate (methotrexate, MTA, or LY309887) 6 h prior to administration of 5-fluorouracil resulted in additive tumor growth delay (TGD) of the MX-1 tumor when the antifolate was methotrexate or LY309887 and greater-than-additive tumor growth delay when the antifolate was MTA. In the H460 tumor, the most effective regimens were a 14-day course of MTA or LY309887 along with 5-fluorouracil administered on the final 5 days. In addn., the simultaneous combination of MTA administered daily for 5 days for 2 wk with administration of gemcitabine resulted in greater-than-additive H460 TGD. MTA was additive with fractionated radiation therapy in the H460 tumor when the drug was administered prior to each radiation fraction. MTA administered with paclitaxel produced greater-than-additive H460 TGD, and additive responses with vinorelbine and carboplatin. In the Calu-6 non-small-cell lung carcinoma xenograft, MTA administered in combination with cisplatin or oxaliplatin was highly effective, whereas MTA administered in combination with cyclophosphamide, gemcitabine, or doxorubicin produced additive responses. Administration of MTA with paclitaxel or doxorubicin resulted in additive MX-1 TGD. Thus, MTA appears to be esp. effective in combination therapies including 5-fluorouracil or an antitumor Pt complex.

Answer 61:

Bibliographic Information

Development of human lymphoma/leukemia xenograft models in immune-deficient mice for evaluation of potential anticancer agents. Dykes, D. J.; Hollingshead, M. G.; Camalier, R. F.; Waud, W. R.; Mayo, J. G. Southern Research Institute, Birmingham, AL, USA. Contributions to Oncology (1999), 54(Relevance of Tumor Models for Anticancer Drug Development), 295-304. Publisher: S. Karger AG, CODEN: COONEV ISSN: 0250-3220. Journal written in English. CAN 133:217399 AN 2000:242563 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Eleven human lymphoma/leukemia cell lines were assessed as in vivo xenograft models in severe combined immunodeficient (SCID) mice. In prepn. for efficacy evaluations of new antitumor agents, all eleven cell lines have been characterized for sensitivity to known clin. useful agents. The lines included in the study represent a variety of diseases including T-cell, myelogenous, and lymphoblastic leukemias, as well as histiocytic, B-cell and Burkitt's lymphomas. The selected agents for this study were representative of various chem. classes. Addnl., growth studies were performed including comparisons in athymic nude mice. These studies were designed to det. s.c. tumor vol. doubling times, graft success, latent growth periods, and other characteristics necessary to effectively implement and interpret anticancer efficacy evaluations. The various tumor lines used proved to be good models for chemotherapy trials. In the chemotherapy trials, considerable independent chemotherapeutic profiles were obsd. but there were also some similarities among the various histol. types.

Answer 62:

Bibliographic Information

Sphingomyelin potentiates chemotherapy of human cancer xenografts. Modrak, David E.; Lew, Walter; Goldenberg, David M.; Blumenthal, Rosalyn. Garden State Cancer Center, Belleville, NJ, USA. Biochemical and Biophysical Research Communications (2000), 268(2), 603-606. Publisher: Academic Press, CODEN: BBRCA9 ISSN: 0006-291X. Journal written in English. CAN 132:260313 AN 2000:115075 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We propose that one manifestation of altered sphingolipid metab. within tumor cells may be a reduced sensitivity to anti-cancer therapies because of an inability to produce a sufficient apoptotic signal via sphingomyelin hydrolysis to ceramide. If so, then sphingomyelin administration could reverse this effect and increase a tumor's sensitivity to chemotherapy. In vivo, i.v. sphingomyelin (10 mg/day, 7 days) potentiated 5-fluorouracil chemotherapy (0.45 mg/day, 5 days) when co-administered to HT29 human colonic xenograft-bearing nude mice. In vitro, sphingomyelin (SM) at its max. tolerated concn. increased 5-fluorouracil and doxorubicin sensitivity of HCT15 and MOSER (1 mg/mL SM) and LS174T and SW480 human colonic tumor cells (0.1 mg/mL) approx. 100-300%. At 1 mg/mL SM, however, no effect was seen using HT29, LoVo and WiDr cells. There was no sensitization of normal human umbilical cord endothelial cells. Thus, sphingomyelin co-administration may be one method to improve the selective efficacy of chemotherapy in some tumors, possibly through enhancement of the apoptotic response. (c) 2000 Academic Press.

Answer 63:

Bibliographic Information

Induction of apoptosis in metastatic foci from human gastric cancer xenografts in nude mice and reduction of circulating tumor cells in blood by 5-FU and 1-hexylcarbamoyl-5-fluorouracil. Nakanishi, Hayao; Abe, Atsushi; Inada, Kenichi; Tsukamoto, Tetsuya; Yasui, Kenzo; Tatematsu, Masae. Laboratory Pathology, Research Institute, Aichi Cancer Center, Nagoya, Japan. Journal of Cancer Research and Clinical Oncology (1999), 125(12), 660-668. Publisher: Springer-Verlag, CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 132:198 AN 1999:759921 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antimetastatic effects of 5-FU and its deriv., 1-hexylcarbamoyl-5-fluorouracil (HCFU) on human gastric cancer micrometastasis and their mode of action were evaluated, using a spontaneous lung metastasis model (HY-1) in nude mice. Metastases were 1st detected in the lung from 4 wk after s.c. transplantation, growing intravascularly and forming micrometastases at 100% incidence by 6 wk after implantation. Lung metastasis in mice bearing s.c. tumors was inhibited by HCFU at doses of 100-150 mg kg-1 day-1 without severe toxic side-effects, when orally administered 3 times per wk either from week 4 or week 6 to 9 wk after implantation. Spontaneous lung metastasis was also inhibited by the administration of 5-FU, but to lesser extent than with HCFU at equimolar low doses. Apoptosis within primary tumors and lung metastatic foci, as detected by the terminal-deoxynucleotidyltransferase-mediated dUTP nick-end labeling method, was found to be enhanced by HCFU as well as 5-FU administration at doses of >100 mg kg-1 day-1 and 50 mg kg-1 day-1 resp. However, proliferating activity of the metastatic foci, as evaluated by MIB-1 immunostaining, was not suppressed by HCFU or 5-1 V treatment. Furthermore, polymerase chain reaction anal. using human specific primers for the β-globin gene, which proved to be capable of detecting 10 tumor cells/mL mouse blood, revealed that circulating tumor cells in the peripheral blood of mice bearing primary tumors were reduced by HCFU or 5-FU administration. These results indicate that circulating tumor cells in blood and micrometastases in the lung are sensitive to these chemotherapeutic agents, and suggest that the anti-metastatic effect of these agents is mediated, at least in part, by enhanced apoptosis rather than by inhibition of cell proliferation.

Answer 64:

Bibliographic Information

Radioimmunotherapy of colorectal cancer in small volume disease and in an adjuvant setting: preclinical evaluation in comparison to equitoxic chemotherapy and initial results of an ongoing phase-I/II clinical trial. Behr, Thomas M.; Memtsoudis, Stavros; Vougioukas, Vassilios; Liersch, Torsten; Gratz, Stefan; Schmidt, Florian; Lorf, Thomas; Post, Stefan; Wormann,

Bernhard; Hiddemann, Wolfgang; Ringe, Burckhardt; Becker, Wolfgang. Department of Nuclear Medicine, University of Gottingen, Gottingen, Germany. Anticancer Research (1999), 19(4A), 2427-2432. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 131:211035 AN 1999:584520 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The 5-yr survival of colorectal cancer patients with distant metastases is below 30%, despite the development and use of a variety of chemotherapeutic regimens. Therefore, new therapeutic strategies are warranted. Whereas radioimmunotherapy (RIT) has shown disappointing results in bulky disease, it may be a promising therapeutic alternative in limited and small vol. disease. The aim of this study was, therefore, to compare, in a preclin. study, the therapeutic efficacy of RIT in colorectal cancer to equitoxic chemotherapy, as well as to evaluate, in a pilot clin. trial, its efficacy in small vol. disease. Nude mice, bearing s.c. or metastatic human colon cancer xenografts, were injected either with the unlabeled or 131I-labeled monoclonal antibodies (MAbs), CO17-1A (which is a murine IgG2a directed against a 41 kDa membrane glycoprotein) or F023C5 (which is an anti-CEA MAb of murine IgG1 subtype), or were administered 5-fluorouracil / folinic acid (5-FU/LV) at equitoxic doses. In a pilot clin. study, 10 colorectal cancer patients with small vol. metastatic disease (all lesions $\leq$ 3 cm) have been entered so far in an ongoing mCi/m2-based dose escalation study with the 131I-labeled F023C5. In the animals, the max. tolerated activities (MTD) of 131I-labeled CO17-1A and F023C5 were 300 μCi and 600 μCi, resp., corresponding to blood doses of approx. 15 Gy each. Accordingly, myelotoxicity was dose-limiting. The MTD in the chemotherapy group was 0.6 mg 5-FU / 1.8 mg LV, given as i.v. bolus 1 h apart for 5 subsequent days. Whereas no significant therapeutic effects were seen with both unlabeled MAbs or 5-FU/LV chemotherapy, tumor growth was retarded significantly with both radiolabeled antibodies. In the metastatic model, chemotherapy prolonged life for only a few weeks, whereas RIT led to cures in 35-55% of the animals. As was the case in the animals, myelotoxicity seems to be dose-limiting in patients as well. Encouraging anti-tumor effects were obsd., lasting for up to more than 12 mo.

These data suggest that radioimmunotherapy may be a viable therapeutic option in colorectal cancer patients with limited disease. Myelotoxicity is the only dose-limiting organ toxicity. Although most patients were treated below the MTD, anti-tumor effects are encouraging. Further studies are ongoing.

Answer 65:

Bibliographic Information

Antitumor activity and novel DNA-self-strand-breaking mechanism of CNDAC (1-(2-C-cyano-2-deoxy-β-D-arabino-pentofuranosyl)cytosine) and its N4-palmitoyl derivative (CS-682). Hanaoka, Kenji; Suzuki, Masako; Kobayashi, Tomowo; Tanzawa, Fumie; Tanaka, Kazuo; Shibayama, Takahiro; Miura, Shinichi; Ikeda, Tomoko; Iwabuchi, Haruo; Nakagawa, Akihiko; Mitsuhashi, Yoshihiro; Hisaoka, Masashi; Kaneko, Masakatsu; Tomida, Akihiro; Wataya, Yusuke; Nomura, Tatsuji; Sasaki, Takuma; Matsuda, Akira; Tsuruo, Takashi; Kurakata, Shinichi. Biological Research Laboratories, Sankyo Co., Ltd., Tokyo, Japan. International Journal of Cancer (1999), 82(2), 226-236. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 131:266648 AN 1999:438485 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have studied the antitumor activity and the novel DNA-self-strand-breaking mechanism of CNDAC (1-(2-C-cyano-2-deoxy-β-D-arabino-pentofuranosyl)cytosine) and its N4-palmitoyl deriv. (CS-682). In vitro, CS-682 showed strong cytotoxicity against human tumor cells comparable with that of CNDAC; both compds. displayed a similar broad spectrum. In vivo, however, orally administered CS-682 showed a more potent activity against human tumor xenografts than CNDAC, 5'-deoxy-5-fluorouridine, 5-fluorouracil and 2',2'-difluorodeoxycytidine. Moreover, CS-682 was effective against various human organ tumor xenografts at a wide dose range and with low toxicity, and was effective against P388 leukemic cells resistant to mitomycin-C, vincristine, 5-fluorouracil or cisplatin in syngeneic mice. CNDAC, an active metabolite of CS-682, had a prolonged plasma half-life after repeated oral administrations of CS-682 but not after oral administrations of CNDAC itself. This difference may partially explain the higher antitumor activity of CS-682 relative to CNDAC. In both CNDAC- and CS-682-treated carcinoma cells, CNDAC 5'-triphosphate (CNDACTP) was generated and incorporated into a DNA strand. High performance liq. chromatog. (HPLC) and mass spectrometric anal. of the nucleosides prepd. by digestion of the DNA from the CNDAC-treated cells detected ddCNC (2'-C-cyano-2',3'-didehydro-2',3'-dideoxycytidine), which was shown to be generated only when the self-strand-breakage of

CNDACTP-incorporated DNA occurred. The cytotoxicity of CNDAC was completely abrogated by the addn. of 2'-deoxycytidine and was low against cells with decreased deoxycytidine kinase. Our results suggest that CNDAC is converted to CNDACMP by deoxycytidine kinase and that the resulting CNDACTP incorporated into a DNA strand as CNDACMP may induce DNA-self-strand-breakage. This novel DNA-self-strand-breaking mechanism may contribute to the potent antitumor activity of CS-682.

Answer 66:

Bibliographic Information

MTA (LY231514) in combination treatment regimens using human tumor xenografts and the EMT-6 murine mammary carcinoma. Teicher, Beverly A.; Alvarez, Enrique; Liu, Pocheng; Lu, Ku; Menon, Krishna; Dempsey, Jack; Schultz, Richard M. Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, USA. Seminars in Oncology (1999), 26(2, Suppl. 6), 55-62. Publisher: W. B. Saunders Co., CODEN: SOLGAV ISSN: 0093-7754. Journal written in English. CAN 131:125026 AN 1999:290814 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

An important component in the development of a new anticancer drug is an understanding of its potential for inclusion in combination treatment regimens. LY231514, a multitargeted antifolate (MTA), was tested in combination with cisplatin, methotrexate, 5-fluorouracil, paclitaxel, docetaxel, doxorubicin, LY329201 (a glycinamide ribonucleotide formyl-transferase [GARFT] inhibitor), and fractionated radiation therapy in vivo using EMT-6 mammary carcinoma, human HCT 116 colon carcinoma, and human H460 non-small cell lung carcinoma grown as xenografts in nude mice. Isobologram methodol. was used to det. the additivity or synergy of the combination regimens. MTA administered with cisplatin, paclitaxel, docetaxel, or fractionated radiation therapy produced additive to greater than additive tumor response by tumor cell survival assay and tumor growth delay. While an additive tumor response was obsd. when MTA was administered with methotrexate, synergistic tumor responses were seen when MTA was administered with the GARFT inhibitor, LY329201, or with the topoisomerase I inhibitor, irinotecan. MTA was administered in combination with full doses of each anticancer agent studied, with no evidence of increased toxicity resulting from the combination.

Answer 67:

Bibliographic Information

Dihydropyrimidine dehydrogenase activity and messenger RNA level may be related to the antitumor effect of 5-fluorouracil on human tumor xenografts in nude mice. Ishikawa, Yoichiro; Kubota, Tetsuro; Otani, Yoshihide; Watanabe, Masahiko; Teramoto, Tatsuo; Kumai, Koichiro; Kitajima, Masaki; Takechi, Teiji; Okabe, Hiroyuki; Fukushima, Masakazu. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. Clinical Cancer Research (1999), 5(4), 883-889. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 131:97096 AN 1999:277434 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We investigated the correlation between tumor sensitivity to 5-fluorouracil (5-FU) and the enzymic activity and mRNA levels of thymidylate synthetase (TS) and dihydropyrimidine dehydrogenase (DPD) using human tumor xenografts in nude mice. Three gastric carcinoma xenografts (SC-1-NU, St-4, and H-111), two colon carcinoma xenografts (Co-4 and Col-3-JCK), one pancreatic carcinoma xenograft (PAN-3-JCK), and one breast carcinoma xenograft (MX-1) were inoculated into nude mice. When the resultant tumors reached 100-300 mg, 5-FU was administered i.p. at a dose of 60 mg/kg in a schedule of three times every 4 days, and the antitumor activity of 5-FU was evaluated as the relative mean tumor wt. in treated mice compared to control mice. Xenografts were also inoculated into untreated nude mice. When tumors weighed 200-300 mg, tumor tissues were resected for measurement of tumoral TS and DPD. TS and DPD activities were detected by the TS-binding assay and a radioenzymic assay, resp. MRNA levels were measured by semiquant. reverse transcription-PCR, with glyceraldehyde-3-phosphate dehydrogenase coamplified as an internal std. TS and DPD activities ranged from 84.7 to 775.5 fmol/mg protein and from not detectable to 79.7 pmol/min/mg protein, resp. TS and

DPD mRNA levels ranged from 0.51 to 9.90 and from not detectable to 0.93, resp. The enzymic activities of TS and DPD were correlated with obsd. mRNA levels. DPD levels were significantly correlated with 5-FU sensitivity, with high DPD activity and high DPD mRNA level resulting in low sensitivity to 5-FU. In contrast, no correlation between TS level and 5-FU sensitivity was obsd. Tumoral DPD activity and DPD mRNA level may be useful indicators in predicting the antitumor activity of 5-FU.

Answer 68:

Bibliographic Information

Relationship between protein levels and gene expression of dihydropyrimidine dehydrogenase in human tumor cells during growth in culture and in nude mice. Takechi, Teiji; Okabe, Hiroyuki; Fujioka, Akio; Murakami, Yuko; Fukushima, Masakazu. Cancer Research Laboratory, Hanno Research Center, Taiho Pharmaceutical Co., Ltd., Hanno-city, Japan. Japanese Journal of Cancer Research (1998), 89(11), 1144-1153. Publisher: Japanese Cancer Association, CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 130:151802 AN 1998:798306 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Protein levels and gene expression of dihydropyrimidine dehydrogenase (DPD), the rate-limiting enzyme for degrdn. of 5-fluorouracil, were studied in two human tumor cell lines (fibrosarcoma HT-1080 and pancreatic carcinoma MIAPaCa-2) in various growth phases of the cultured cells and of tumor xenografts implanted into nude mice. DPD catalytic activity and DPD protein content in cytosolic prepns. were detd. by means of radioenzymic assay and western blot anal., resp. Relative DPD mRNA expression was detd. by using a semi-quant. reverse transcription-polymerase chain reaction in which glyceraldehyde-3-phosphate dehydrogenase mRNA was used as an internal std. DPD activity and protein content in cultures of both cell lines increased in proportion to cell d. (DPD activities ranged from undetectable to 84 pmol/min/mg protein in the HT-1080 cells and from undetectable to 335 pmol/min/mg protein in the MIAPaCa-2 cells). DPD mRNA levels, on the other hand, tended to decrease slightly during cell growth. DPD activity and protein content in HT-1080 tumor xenografts increased during growth in proportion to tumor wt. (DPD activities ranged from 7 to 131 pmol/min/mg protein), but DPD mRNA levels did not correlate with tumor wt. DPD activity and protein content in MIAPaCa-2 tumor xenografts did not change much, and seemed to have already plateaued, since the tumors were small (weighing about 30 mg). These findings suggest that DPD protein expression during tumor growth is controlled at the post-transcriptional level.

Answer 69:

Bibliographic Information

Antitumor activity of SCH 66336, an orally bioavailable tricyclic inhibitor of farnesyl protein transferase, in human tumor xenograft models and wap-ras transgenic mice. Liu, Ming; Bryant, Matthew S.; Chen, Jianping; Lee, Suining; Yaremko, Bohdan; Lipari, Phil; Malkowski, Michael; Ferrari, Eric; Nielsen, Loretta; Prioli, Nicholas; Dell, Janet; Sinha, Dineshwar; Syed, Jameel; Korfmacher, Walter A.; Nomeir, Amin A.; Lin, C-C.; Wang, Lynn; Taveras, Arthur G.; Doll, Ronald J.; Njoroge, F. George; Mallams, Alan K.; Remiszewski, Stacy; Catino, Joseph J.; Girijavallabhan, Viyyoor M.; Kirschmeier, Paul; Bishop, W. Robert. Departments of Biological Research-Oncology, Schering-Plough Research Institute, Kenilworth, NJ, USA. Cancer Research (1998), 58(21), 4947-4956. Publisher: AACR Subscription Office, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 130:104933 AN 1998:728126 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have been developing a series of nonpeptidic, small mol. farnesyl protein transferase inhibitors that share a common tricyclic nucleus and compete with peptide/protein substrates for binding to farnesyl protein transferase. Here, we report on pharmacol. and in vivo studies with SCH 66336, a lead compd. in this structural class. SCH 66336 potently inhibits Ha-Ras processing in whole cells and blocks the transformed growth properties of fibroblasts and human tumor cell lines expressing activated Ki-Ras proteins. The anchorage-independent growth of many human tumor lines that lack an activated ras oncogene is also blocked by treatment with SCH 66336. In mouse, rat, and monkey systems, SCH 66336 has excellent oral bioavailability and pharmacokinetic properties. In the nude mouse, SCH 66336 demonstrated potent oral activity in a wide array of human tumor xenograft models including tumors of colon,

lung, pancreas, prostate, and urinary bladder origin. Enhanced in vivo efficacy was obsd. when SCH 66336 was combined with various cytotoxic agents (cyclophosphamide, 5-fluorouracil, and vincristine). In a Ha-Ras transgenic mouse model, prophylactic treatment with SCH 66336 delayed tumor onset, reduced the av. no. of tumors/mouse, and reduced the av. tumor wt./animal. In a therapeutic mode in which gavage treatment was initiated after the transgenic mice had developed palpable tumors, significant tumor regression was induced by SCH 66336 in a dose-dependent fashion. This was assocd. with increased apoptosis and decreased DNA synthesis in tumors of animals treated with SCH 66336. Enhanced efficacy was also obsd. in this model when SCH 66336 was combined with cyclophosphamide. SCH 66336 is presently being evaluated in Phase I clin. trials.

Answer 70:

Bibliographic Information

The alkylator treosulfan shows activity towards human renal-cell carcinoma in vivo and in vitro. Koepf-Maier, P. Institut fuer Anatomie, Freie Universitaet Berlin, Berlin, Germany. In Vivo (1998), 12(3), 275-288. Publisher: International Institute of Anticancer Research, CODEN: IVIVE4 ISSN: 0258-851X. Journal written in English. CAN 129:285676 AN 1998:550055 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Treosulfan (L-threitol-1,4-bismethanesulfonate, Ovastat) was tested on human renal tumor cells growing as xenografts in athymic nude mice and as monolayers in vitro, in comparison with clin. used cytostatic drugs (in vivo, cyclophosphamide, vinblastine, and 5-fluorouracil; in vitro, vinblastine and 5-fluoro-2'-deoxyuridine) which were administered at equitoxic or equiv. dose levels, resp. Four human renal tumor xenografts (N-U 2, N-U 26, MRI-H 121, KTCTL-1M) were investigated in vivo, and seven renal tumor cell lines (KTCTL-1M, KTCTL-2, KTCTL-26A, KTCTL-30, KTCTL-84, MRI-H 121, N-U 2) under in vitro conditions. The investigations of the four human renal tumor xenografts revealed that treosulfan is capable of inducing pronounced growth inhibitions ranging from 60-100% in comparison with untreated control tumors. In the xenografted renal-cell carcinoma KTCTL-1M, treosulfan administered at the highest dose level (1 × 3500 mg/kg) even effected a complete remission lasting for more than three weeks in all animals treated with this dose. It was more effective in the N-U 2 carcinoma growing in vivo than the comparative compds. cyclophosphamide and vinblastine. In the heterotransplanted renal-cell carcinoma N-U 26, treosulfan showed a similar activity as the two established cytostatic drugs tested whereas, in the renal sarcoma MRI-H 121, both cyclophosphamide and vinblastine were slightly more effective than treosulfan. In four renal-cell carcinomas growing as monolayers in vitro (KTCTL-1M, KTCTL-2, KTCTL-84, N-U 2), treosulfan induced cell growth inhibitions by about 50% at peak plasma concn. in comparison with untreated control cultures. The IC50 values ranged from 5 × 10-6 to 10-4 mol/L in all seven monolayer cultures investigated. 5-Fluoro-2'-deoxyuridine (floxuridine) was similarly active in vitro as treosulfan with respect to the molar concns.

inducing growth inhibition and to the IC50 values, whereas vinblastine was more effective than treosulfan in most of the human renal tumor cell monolayers investigated. These results reveal the remarkable antitumor efficacy of treosulfan toward human renal-cell carcinomas, esp. under in vivo conditions. This activity was similarly high or even better than in cyclophosphamide and vinblastine. The in vitro data obtained in monolayer cultures also confirmed the remarkable antiproliferative activity of treosulfan in renal tumor cells, but did not mirror very well the pattern of antitumor activity obsd. in vivo.

Answer 71:

Bibliographic Information

Chemosensitivity of human pancreatic cancer cell lines serially transplanted in nude mouse. Tomikawa, Moriaki; Kubota, Tetsuro; Takahashi, Shin; Matsuzaki, Shinjiro Wilson; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. Anticancer Research (1998), 18(2A), 1059-1062. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 129:156567 AN 1998:396377 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic cancer frequently recurs or metastasizes even after apparently curative surgical resection. Because of a low, five-year survival rate after radical surgery, multi-modal adjuvant treatment must be used to prevent recurrence of systemic spread. The effectiveness of the exptl. cancer chemotherapy of mitomycin C (MMC), cisplatin (DDP), doxorubicin (DXR) and 5-fluorouracil (5-FU) was evaluated in three human pancreatic cancer xenografts serially transplanted in nude mice. When the effects of these agents were evaluated by 3-(4,5-dimethylthiazol-2yl)-2,5-diphenyl-2H tetrazolium bromide (MTT) assay, only MMC and DDP were effective on PAN-3-JCK, a poorly differentiated adenocarcinoma. When PAN-12-JCK, a moderately differentiated adenocarcinoma, was used an in vitro assessment of combined chemotherapy of MMC and DDP, a synergistic combination effect was obsd. Three xenografts were transplanted s.c. into nude mice and the max. tolerated doses of these agents were administered i.p. or i.v. (DXR). MMC showed pos. antitumor activity on PAN-3-JCK and PAN-12-JCK, and 5-FU was effective on PAN-12-JCK. These results reflect the low sensitivity of clin. pancreatic cancer to conventionally available antitumor agents, and suggest the possible synergistic combination antitumor activity of MMC and DDP.

Answer 72:

Bibliographic Information

Enhancement of anticancer effects of radiation and conventional anticancer agents by a quinolinone derivative, vesnarinone: studies on human gastric cancer tissue xenografts in nude mice. Kawai, Kazuyoshi; Konishi, Yasue; Izumi, Kazunari; Sato, Mitsunobu; Adachi, Masakazu; Hozumi, Motoo. Cellular Technology Institute, Otsuka Pharmaceutical Company, Tokushima, Japan. Anticancer Research (1998), 18(1A), 405-412. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 128:318901 AN 1998:282108 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Vesnarinone (3,4-dihydro-6-[4-(3,4-dimethoxybenzoyl)-1-piperazinyl]-2(1H)-quinolinone), a quinolinone deriv., is an orally active inotropic agent used in Japan for the treatment of chronic heart failure. Recently, it has been reported that vesnarinone induces differentiation and apoptosis in certain types of leukemia and solid tumor cells, and exhibits antitumor effect on several tumors xenografted in nude mice. In the present study, we examd. the antitumor effect of vesnarinone in combination with radiation and conventional anticancer agents in nude mice xenografted with human gastric carcinoma, a poorly-differentiated adenocarcinoma, MKN-45 cell line which has a wild-type p53 gene. Vesnarinone treatment combined with radiation resulted in a higher antitumor activity compared with a single treatment with either vesnarinone or radiation alone. Further, vesnarinone treatment together with radiation and conventional anticancer agents including 5-FU and picibanil (an immunopotentiator) produced the highest antitumor effect compared with any other treatment. Addnl., the combination treatment induced marked differentiation and apoptosis of the tumor cells and an increase in the expression of p53 gene in the treated tumor cells. The results suggest that vesnarinone, in combination with radiation and the conventional antitumor agents, may be of clin. interest for treatment of certain types of gastric tumors.

Answer 73:

Bibliographic Information

Methionine-depletion modulates the efficacy of 5-fluorouracil in human gastric cancer in nude mice. Hoshiya, Yasunori; Kubota, Tetsuro; Inada, Takao; Kitajima, Masaki; Hoffman, Robert M. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. Anticancer Research (1997), 17(6D), 4371-4375. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 128:265845 AN 1998:200665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human tumors are generally methionine (MET)-dependent in that their growth is inhibited by MET-depletion down to levels that will still allow normal cell growth. The differential effect of methionine depletion on tumor and normal cells has suggested that methionine depletion may be able to modulate many and possibly all classes of cancer drugs. In this report, the authors detd. if MET-depletion could modulate 5-fluorouracil (5-FU) efficacy on the human gastric cancer xenograft, SC-1-NU in nude mice. The tumor-bearing mice were treated with a MET-free diet and i.p. administration of 5-FU at a dose of 30 mg/kg given for four cycles. MET depletion enhanced

the antitumor activity of 5-FU by approx. two-fold with statistical significance of. The MET-free diet increased intratumoral thymidylate synthetase inhibition early after 5-FU administration; therefore, MET-depletion was thought to increase the 5-FU antitumor activity by modulating intratumoral folate metab. The data in this report suggest the high clin. potential of methionine depletion, combined with 5-FU and leucovorin on refractory tumors such as stomach cancer.

Answer 74:

Bibliographic Information

Pharmacokinetic optimization of the treatment of cancer with high dose zidovudine. Danesi, Romano; Falcone, Alfredo; Conte, Pier Franco; Del Tacca Mario. Division of Pharmacology and Chemotherapy, Department of Oncology, University Hospital, Pisa, Italy. Clinical Pharmacokinetics (1998), 34(2), 173-180. Publisher: Adis International Ltd., CODEN: CPKNDH ISSN: 0312-5963. Journal; General Review written in English. CAN 128:252365 AN 1998:152135 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review with 24 refs. The thymidine analog zidovudine is currently used for the treatment of HIV-infected patients, as the early development of the drug as an anticancer agent yielded modest results. A comprehensive preclin. anal., however, showed that inhibitors of de novo thymidylate synthesis, including fluorouracil and methotrexate, enhanced the antiproliferative activity of zidovudine in cancer cells. Significant inhibition of tumor growth was obtained in mice bearing human colon cancer xenografts and given i.p. zidovudine 300 to 600 mg/kg weekly in combination with methotrexate 87.5 mg/kg or i.p. fluorouracil 85 mg/kg, and in pharmacokinetic studies high peak drug plasma concns. (Cmax) of zidovudine were obtained, ranging from 610.3 to 1698.8 μmol/L. In order to exploit the therapeutic activity of zidovudine, phase I and II clin. studies were designed in combination with fluorouracil and the pharmacokinetic-pharmacodynamic profile of zidovudine was investigated. Clin. responses were obtained in patients treated i.v. with bolus fluorouracil 500 mg/m2, leucovorin and short (90 to 120 min) infusions of high dose zidovudine (up to 10 g/m2), generating drug Cmax similar to those obtained in preclin. models. However, in chemotherapy-pretreated patients receiving high dose zidovudine by the oral route (1 to 9 g/m2/day) or 48-hourly continuous i.v. infusion (2 to 20 g/m2/day) in combination with fluorouracil and leucovorin, treatment failures were obsd. despite high systemic exposure, described as the area under the plasma concn.-time curve and the occurrence of DNA strand breaks in peripheral blood mononucleated cells, the biol. expression of zidovudine activity. In conclusion, preclin. and clin. evidence suggest that the schedule of administration of zidovudine is a requisite for the expression of its activity, indicating the importance of concn.-monitored trials to optimize chemotherapy dose administration in patients.

The likelihood of tumor response appears to be related to the achievement of high peak plasma concns. of zidovudine, and const. infusions appear less likely to produce clin. results.

Answer 75:

Bibliographic Information

A pharmacokinetic and pharmacodynamic study in vivo of human HT29 tumors using 19F and 31P magnetic resonance spectroscopy. Mcsheehy, P. M. J.; Seymour, M. T.; Ojugo, A. S. E.; Rodrigues, L. M.; Leach, M. O.; Judson, I. R.; Griffiths, J. R. CRC Biomedical Magnetic Resonance Research Unit, Department of Cell and Molecular Sciences, St. George's Hospital Medical School, London, UK. European Journal of Cancer (1997), 33(14), 2418-2427. Publisher: Elsevier Science Ltd., CODEN: EJCAEL ISSN: 0959-8049. Journal written in English. CAN 128:200652 AN 1998:70564 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

19F-MRS (magnetic resonance spectroscopy) was used to study the pharmacokinetics of 5-fluorouracil (5-FU) in human (HT29) tumor xenografts, with and without pretreatment of the mice using either thymidine (40 min) or interferon-α (2 and 24 h). A 200 mg/kg i.p. bolus dose of 5-FU was eliminated from control tumors with a t1/2 of 25.4 ± 2 min (mean ± SEM, n = 11), while both thymidine (500 mg/kg) and interferon (50 000 IU/mouse) significantly increased t1/2 to 36.5 ± 6.1 (n = 5) and 48.1 ± 13.6 min (n = 4), resp. (P = 0.04,

Gabriel's ANOVA). Thymidine increased 5-FU anabolism to cytotoxic 5-fluoronucleotides, and decreased the amt. of tumor catabolites; the latter probably recirculated from liver since isolated HT29 cells did not catabolize 5-FU. These in vivo observations were confirmed by 19F-MRS quantification of tumor exts. Interferon did not significantly affect 5-FU metab. in the tumor or liver, nor the 5-FU t1/2 in liver. Treatment of tumors with 5-FU or interferon had no effect on tumor growth, whereas the combination strongly inhibited growth. 31P-MRS of HT29 tumors showed that 2 and 24 h after i.p. injections of interferon there was a significant increase in the pHint of 0.3 ± 0.04 units (P = 0.002), while pHext and the tumor NTP/Pi ratio were unchanged. The large increase in the neg. pH gradient (-Δ pH) across the tumor plasma membrane caused by interferon suggests the Δ pH may be a factor in tumor retention of 5-FU, as recently shown in isolated tumor cells.

Answer 76:

Bibliographic Information

Improved treatment of medullary thyroid cancer in a nude mouse model by combined radioimmunochemotherapy: doxorubicin potentiates the therapeutic efficacy of radiolabeled antibodies in a radioresistant tumor type. Behr, Thomas M.; Wulst, Erik; Radetzky, Sven; Blumenthal, Rosalyn D.; Dunn, Robert M.; Gratz, Stefan; Rave-Frank, Margret; Schmidberger, Heinz; Raue, Friedhelm; Becker, Wolfgang. Department of Nuclear Medicine, Georg-August-University, Gottingen, Germany. Cancer Research (1997), 57(23), 5309-5319. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 128:99359 AN 1997:775899 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Whereas in advanced metastatic medullary thyroid cancer (MTC), a variety of chemotherapeutic regimens have achieved only limited success clin., more recently, radioimmunotherapy (RIT) with 131I-labeled anti-carcinoembryonic antigen (CEA) monoclonal antibodies (MAbs) has shown promising results. The aims of this study were to compare, in an animal model, the therapeutic efficacy of RIT to clin. used "std." chemotherapeutic regimens and to evaluate whether combination strategies of both modalities may be feasible and may help to improve therapeutic results in this rather radioresistant tumor type. Nude mice, bearing s.c. xenografts of the human MTC cell line, TT, were treated either with the 131I-labeled anti-CEA MAb, F023C5 IgG, or were administered chemotherapeutic regimens that had shown promising results in patients with metastatic MTC (doxorubicin and cisplatinum monotherapy, combinations of both agents, and a 5-fluorouracil/dacarbazine/streptozotocin scheme). Control groups were left untreated or were injected with an irrelevant radiolabeled antibody at equitoxic dose levels. The max. tolerated dose (MTD) of each agent was detd. Combinations of chemotherapy and RIT were evaluated as well. Toxicity and tumor growth were monitored at weekly intervals. From the chemotherapeutic agents and schemes tested, doxorubicin monotherapy was the most effective; combination therapies did not result in an increased antitumor efficacy, but they did result in more severe toxicity. At equitoxic doses, no significant difference was found between the therapeutic efficacy of doxorubicin and that of RIT. Myelotoxicity was dose limiting with radiolabeled MAbs (MTD, 600 μCi), as well as with chemotherapeutic regimens contg. alkylating agents (cisplatinum, dacarbazine, or streptozotocin). At its MTD (200 μg), doxorubicin caused only mild myelotoxicity, and despite signs of cardiac toxicity, gastrointestinal side effects were dose limiting. Accordingly, bone marrow transplantation (BMT) enabled dose intensification with RIT (MTD with BMT, 1100 μCi), which led to further increased antitumor efficacy, whereas BMT was unable to increase the MTD of doxorubicin. Due to the complementarity of toxic side effects but an anticipated synergism of antitumor efficacy, combinations of RIT with doxorubicin were tested. Administrations of 500 μCi of 131I-labeled anti-CEA and, 48 h later, 200 μg of doxorubicin (i.e., 83 and 100% of the resp. single-agent MTDs), were the highest doses that did not result in an increased lethality; with bone marrow support, 1000 μCi of 131I-labeled anti-CEA could be combined with 200 μg of doxorubicin (i.e., 90 and 100% of the individual MTDs). Therapeutic results of this combined radioimmunochemotherapy were superior to equitoxic monotherapy with either agent, and indication for synergistic antitumor effects is given. At its resp. MTD, radioimmunochemotherapy led to a 36% cure rate if it was given without bone marrow support and to a 85% permanent cure rate if it was given with bone marrow support. The animal model, as presented in this study, seems to be useful for the preclin. testing of therapeutic agents for the systemic treatment of MTC. At equitoxic doses, RIT with radiolabeled anti-CEA antibodies seems to be equally as effective as chemotherapy with doxorubicin. Combination of RIT and doxorubicin chemotherapy seems to have synergistic therapeutic efficacy, which may be due to a radiosensitizing effect of doxorubicin.

Answer 77:

Bibliographic Information

5-FU-induced apoptosis correlates with efficacy against human gastric and colon cancer xenografts in nude mice. Inada, Takao; Ichikawa, Akira; Kubota, Tetsuro; Ogata, Yoshiro; Moossa, A. R.; Hoffman, Robert M. The Department of Surgery and Laboratory Tochigi Cancer Center, Uitsunomiya, Japan. Anticancer Research (1997), 17(3C), 1965-1971. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 127:156371 AN 1997:498596 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Apoptosis may be an important mechanism by which cancer cells are killed by certain agents. It is reported here that apoptosis is a key event in the killing of human tumor cells by 5-fluorouracil (5-FU) in vivo. Apoptosis induced by 5-FU was detd. using two human gastrointestinal tumor xenografts serially transplanted into nude mice: a gastric carcinoma (SC-1-NU) highly sensitive to 5-FU and a colon carcinoma (Co-4) less sensitive to 5-FU. Apoptosis was assayed using the terminal deoxynucleotidyl transferase (TdT)-mediated deoxyuridine triphosphate (dUTP)-biotin nick end labeling method in paraffin-embedded tissue sections, and by flow-cytometric anal. Apoptosis-pos. cells increased gradually during treatment. 24 H after the initiation of 5-FU treatment a max., of 15.4 % of the Co-4 cells were apoptotic. 48 H after the initiation of 5-FU treatment, apoptosis was found in 34% of the tumor cells in the SC-1-NU strain. Flow-cytometry demonstrated the increase of S-phase fractions in both strains after the administration of 5-FU, and this coincided with the appearance of apoptotic-pos. cells. Although the intrinsic TS activities of two strains differed, TS activities were markedly suppressed in both strains immediately after the administration of 5-FU. Concn. of 5-FU in RNA (F-RNA) increased gradually in both strains, reaching a max. 24 h after the administration of 5-FU. These results suggest that apoptosis and inhibition of DNA synthesis induced by 5-FU are closely assocd. with its antitumor effect.

Answer 78:

Bibliographic Information

Antitumor effect of S-1 and cisplatin treatment against human gastric cancer xenografted in nude mice. Kondo, Ken; Akiyama, Seiji; Kasai, Yasushi; Kato, Sawako; Kuno, Yasushi; Kataoka, Masato; Ichihara, Tooru; Horisawa, Masumasa; Shirasaka, Tetsuhiko. Dept. Surgery II, Nagoya University School Medicine, Japan. Gan to Kagaku Ryoho (1997), 24(9), 1103-1108. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 127:214668 AN 1997:484469 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The enhanced effects due to the combined use of oral administration of S-1 and i.p. administration of cisplatin (CDDP) were examd. with gastric cancer xenografts (NUGC 4). S-1, a new anticancer drug, was daily administered at 10 mg/kg (qid×5×3 wk). 5-FU level in blood was 1 μg/mL at two hours after the treatment. Antitumor activity was not found in mice with only the CDDP treatment. But antitumor activity by S-1 and daily low-dose (1 mg/kg) or intermittent treatment (5 mg/kg) of CDDP showed better results than daily S-1 treatment. The daily low-dose CDDP treatment showed similar efficacy to the intermittent administration at the same total dose, but the daily low-dose CDDP treatment was better in the light of toxicities. These results suggest that treatment with S-1 and daily low-dose CDDP was effective for gastric cancer.

Answer 79:

Bibliographic Information

Interaction of interleukin-11 (rhIL-11) with cytotoxic therapies in the human HT-29 colon carcinoma. Teicher, Beverly A.; Ara, Gulshan; Northey, David. Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA, USA. International Journal of Oncology (1997), 10(6), 1081-1085. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 127:80030 AN 1997:399232 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytokine interleukin-11 (rhIL-11) has been shown to enhance the recovery of bone marrow, oral epithelium and intestinal crypt cells after cytotoxic insult by anticancer drugs or ionizing radiation. 5-Fluorouracil based chemotherapy and radiation therapy are frequently used in the treatment of colon cancer. Simultaneous exposure of human HT-29 colon carcinoma cells in culture to rhIL-11 and 5-fluorouracil for 24 h resulted in enhanced cell killing of the HT-29 cells with lower concns. (1-10 μM) of 5-fluorouracil compared with the drug alone. Exposure of HT-29 cells to rhIL-11 prior to, during and after radiation delivery did not alter the killing of normally oxygenated or hypoxic HT-29 cells by the radiation. In vivo treatment of nude mice bearing HT-29 colon tumor xenografts with rhIL-11 prior to and during administration of 5-fluorouracil did not alter the killing of the tumor cells or the killing of the bone marrow CFU-GM by the drug. In the tumor growth delay expts., administration of rhIL-11 to nude mice bearing HT-29 colon tumor xenografts did not alter the growth of the tumor and did not alter the response of the tumor to 5-fluorouracil. However, administration of rhIL-11 to these animals increased the response of the tumor to fractionated radiation therapy resulting in a radiation dose-modifying factor of 1.5±0.2. These results indicate that rhIL-11 may be a selective protector of normal tissues without affecting the response of the tumor to therapy.

Answer 80:

Bibliographic Information

ONYX-015, an E1B gene-attenuated adenovirus, causes tumor-specific cytolysis and antitumoral efficacy that can be augmented by standard chemotherapeutic agents. Heise, Carla; Sampson-Johannes, Adam; Williams, Angelica; McCormick, Frank; Von Hoff, Daniel D.; Kirn, David H. ONYX Pharmaceuticals, Richmond, CA, USA. Nature Medicine (New York) (1997), 3(6), 639-645. Publisher: Nature Publishing Co., CODEN: NAMEFI ISSN: 1078-8956. Journal written in English. CAN 127:75621 AN 1997:357147 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The 55-kilodalton (kDa) protein from the E1B-region of adenovirus bind to and inactivates the p53 gene, which is mutated in half of human cancers. We have previously shown that the replication and cytopathogenicity of an E1B, 55-kDa gene-attenuated adenovirus, ONYX-015, is blocked by functional p53 in RKO and U2OS carcinoma lines. We now report that normal human cells were highly resistant to ONYX-015-mediated, replication-dependent cytolysis. In contrast, a wide range of human tumor cells, including numerous carcinoma lines with either mutant or normal p53 gene sequences (exons 5-9), were efficiently destroyed. Antitumor efficacy was documented following intratumoral or i.v. administration of ONYX-015 to nude mouse-human tumor xenografts; efficacy with ONYX-015 plus chemotherapy (cisplatin, 5-fluorouracil) was significantly greater than with either agent alone.

Answer 81:

Bibliographic Information

Continuous cell lines derived from head and neck tumors for mechanistic studies in vitro and in a nude mouse animal model. Knebel, J. W.; Eckardt, A.; Fokas, K.; Aufderheide, M.; Nolte, M. Institute of Experimental Pathology, Hannover Medical School, Hannover, Germany. International Congress Series (1996), 1114(Head and Neck Cancer: Advances in Basic Research), 111-119. Publisher: Elsevier, CODEN: EXMDA4 ISSN: 0531-5131. Journal written in English. CAN 126:54594 AN 1997:37414 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In a series of expts. the authors established and characterized continuous cell lines of different squamous cell carcinomas. The isolated cells grew in epithelial clusters and expressed cytokeratin. Their differentiation pattern and capacity differ to a certain extent. Using these in vitro systems the authors studied the effects of different chemotherapeutic drugs (e.g., MTX, 5-FU, CBDCA and Taxol). Injection of HN SCC-001 cells into nude mice gave rise to serially transplantable s.c. tumors. The cell line as well as the xenotransplants showed the phenotype and genotype characteristics of the primary tumor.

Answer 82:

Bibliographic Information

Dual biochemical modulation therapy using 5-FU, leucovorin and cisplatin on human rectal carcinoma xenografts in nude mouse. Shibusawa, Miki; Takata, Manabu; Kamiyama, Gouichi; Yokoyama, Noboru; Nakao, Kentaroh; Yoshizawa, Hiroto; Choh, Hirotoshi; Yasuda, Naokuni; Tsunoda, Yuko; et al. Dep. Surgery, Showa Univ. Sch. Med., Tokyo, Japan. Gan to Kagaku Ryoho (1996), 23(9), 1149-1152. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 125:185215 AN 1996:545435 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study examd. a combined treatment for colorectal carcinoma, the dual biochem. modulation therapy, consisting of 5-FU, Leucovorin (LV) and Cisplatin (CDDP). We compared the antitumor effects with other treatments: 5-FU alone, CDDP alone and 5-FU with LV. Primary diffuse infiltrated colorectal carcinoma is well known for its biol. malignancy and its lack of response to chemotherapy. We used SRM cells from a cell line of carcinoma of the rectum, and s.c. injected them into nude mice. The antitumor effects were estd. from the growth rate, inhibition rate and thymidylate synthetase inhibition rates in the tumor tissue. Results indicated that even if the concn. of 5-FU and LV were reduced by half, these combined with CDDP were more effective than other therapies. Dual biochem. modulation therapy is particularly promising because the redn. of the dosages would reduce the side effects while still serving as an excellent antitumor therapy.

Answer 83:

Bibliographic Information

An experimental study on antimetabolic action by bolus dosage of 5-fluorouracil, using a human stomach cancer xenograft to nude mice. Hanatani, Yuji; Kodaira, Susumu; Nagaoka, Nobuhiko; Miyoshi, Hiroshi; Asagoe, Tatsuo. Sch. Med., Teikyo Univ., Tokyo, Japan. Nippon Kagaku Ryoho Gakkai Zasshi (1996), 44(7), 557-559. Publisher: Nippon Kagaku Ryoho Gakkai, CODEN: NKRZE5 ISSN: 1340-7007. Journal written in Japanese. CAN 125:237907 AN 1996:520665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The changes in thymidylate synthase (TS) activity and 5-fluorouracil (5-FU) incorporated into RNA (F-RNA) after a bolus dosage of 5-FU were studied using a human stomach cancer xenograft to nude mice (SC-1-NU). The TS inhibition rate (TSIR) reached high levels (40 mg/kg; 93.4%, 10 mg/kg; 74.9%) soon after dosage of 5-FU. F-RNA took 12 h to reach a peak (40 mg/kg; 111 ng/mg-RNA, 10 mg/kg; 21.8 ng/mg-RNA). After the peaks, both TSIR and F-RNA decreased slowly. Esp. at a bolus dosage of 40 mg/kg of 5-FU, TSIR and F-RNA maintained certain levels (TSIR; 40.1%, F-RNA; 31.1 ng/mg-RNA) even at 96 h after dosage of the drug. TSIR and F-RNA increased gradually after successive doses of 5-FU (40 mg/kg q4d and 10 mg/kg qd). Bolus dosage (esp. large doses) of 5-FU showed a prolonged effects on DNA and RNA, suggesting that intermittent bolus dosage of 5-FU could be expected to have good antitumor effects.

Answer 84:

Bibliographic Information

Antitumor activity of menogaril alone, and in combination against human mammary cancer models in mice and rats. Yoshida, Masahiko; Fujioka, Akio; Nakano, Koushi; Kobunai, Takashi; Saito, Hitoshi; Toko, Toshiyuki; Takeda, Setsuo; Unemi, Norio. Anticancer and Antimicrobials Research Laboratory, Taiho Pharmaceutical Co., Ltd., Tokushima, Japan. Anticancer Research (1996), 16(3A), 1155-1159. Publisher: Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 125:185052 AN 1996:472482 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Menogaril is an antitumor agent different from other anthracyclines in being active after oral administration. To predict its clin. effectiveness by this route against human breast cancer, its antitumor activity was compared against breast cancer in exptl. animals with that of injected Adriamycin. Menogaril had half the much antitumor activity of Adriamycin against human mammary cancer cell lines. Menogaril given orally also had a antitumor activity against mammary cancer caused by 7,12-dimethylbenz[a]anthracene in rats comparable with that of adriamycin. The high concn. of menogaril in tumor tissue seemed to contribute to its effectiveness. Of several combinations of cyclophosphamide, Adriamycin, menogaril, and 5-fluorouracil, the combination of cyclophosphamide, menogaril, and 5-fluorouracil was most effective against mouse leukemia L1210 and human breast cancer xenografts in mice. This combination might have antitumor activity against breast cancer superior to that of the therapy currently of 1st choice (cyclophosphamide, Adriamycin, and 5-fluorouracil) in the clinic.

Answer 85:

Bibliographic Information

In vivo/in vitro correlation of xenografts in nude mice and the ATP-cell viability assay. Perras, James P.; Hurst, Josephine. School Medicine, University Miami, Miami, FL, USA. Contributions to Gynecology and Obstetrics (1994), 19(Chemosensitivity Testing in Gynecologic Malignancies and Breast Cancer), 122-131. Publisher: Karger, CODEN: CGOBD6 ISSN: 0304-4246. Journal written in English. CAN 125:131526 AN 1996:450444 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors compare in vitro results of an ATP cell viability assay (ATP-CVA) to the in vivo chemosensitivity of transplanted ovary and breast xenografts in nude mice. This approach not only allows a comparison between the in vitro and in vivo systems, but it also provides a means to compare responses using multiple tumor specimens to evaluate the reproducibility of the ATP- CVA. The results strongly indicate that the ATP-CVA in vitro chemosensitivity assay provides an approach that, to a degree, approximates a clin. situation. With this method, the initial evaluations of in vitro chemosensitivity assays can be done more quickly and easily to compare with in vivo response. It has been shown for 2 xenograft tumors (ovarian and breast) that for those drugs tested, the ATP-CVA can predict the drug sensitivity of these tumors in nude mice. The reproducibility of the ATP-CVA assay is also demonstrated.

Answer 86:

Bibliographic Information

The modulating effect of interferon alpha-2a on the antitumor activity of UFT against a human gastric carcinoma xenograft, SC-1-NU, in nude mice. Kubota, Tetsuro; Kurihara, Naoto; Kase, Suguru; Watanabe, Masahiko; Kumai, Koichiro; Kitajima, Masaki; Inada, Takao. School of Medicine, Keio University, Tokyo, Japan. Surgery Today (1996), 26(1), 12-14. Publisher: Springer, CODEN: SUTOE5 Journal written in English. CAN 124:306730 AN 1996:229275 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The modulating effect of recombinant human interferon alpha-2a (IFN) on the antitumor activity of UFT, a mixed compd. of tegafur and uracil at a molar ratio of 1:4, was investigated against SC-1-NU, a human gastric cancer xenograft serially transplanted in nude mice. IFN was administered s.c. at a dose of 60,000 IU/mouse daily for 14 days, and UFT was given at a dose of 15 mg/kg as tegafur daily, except on Sundays, for 3 wk. The agents were administered either alone or simultaneously. Synergistic antitumor activity on SC-1-NU was produced by the combination of IFN and UFT without any increment of side effects, and the combination therapy also increased intratumoral thymidylate synthetase (TS) inhibition and the amt. of 5-fluorouracil (5-FU) in the intratumoral RNA. Thus, IFN seems to modulate the antitumor activity of UFT against SC-1-NU through an inhibition of DNA synthesis and RNA distortion, and therefore this combination could be useful for clin. application.

Answer 87:

Bibliographic Information

An experimental study on the effect of oral administration of 5-fluorouracil, using a human stomach cancer xenograft in nude mice. Hanatani, Yuji; Kodaira, Susumu; Asagoe, Tatsuo; Miyoshi, Hiroshi; Nagaoka, Nobuhiko. Sch. Med., Teikyo Univ., Tokyo, Japan. Nippon Kagaku Ryoho Gakkai Zasshi (1996), 44(2), 85-9. CODEN: NKRZE5 ISSN: 1340-7007. Journal written in Japanese. CAN 124:219567 AN 1996:171114 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We examd. the antitumor effect of 5-fluorouracil (5-FU) by daily oral (p.o.) administration of 20 mg/kg compared with that by daily i.p. (i.p.) administration of 10 mg/kg. A 5-FU-sensitive human stomach cancer xenograft (SC-1-NU) was used for the expt. We also measured the binding capacity of thymidylate synthase (TS) and 5-FU incorporated into RNA (F-RNA) for the effect on DNA and RNA, resp. Antitumor effects of 5-FU by 20 mg/kg p.o. were significantly stronger than those by 10 mg/kg i.p., throughout the exptl. period ($P < 0.05$). The min. T/C ratios were 9.97% for 20 mg/kg p.o. and 48.1% for 10 mg/kg i.p. The effects of a single dose of 5-FU on TS and R-RNA were transient, whereas the TS inhibition rate and F-RNA content were gradually increased after successive doses of 5-FU. In both cases, no differences were seen between the effects of 20 mg/kg p.o. and 10 mg/kg i.p. It was considered that the effect of a large dose of 5-FU given orally could be equiv. to that given i.p.

Answer 88:

Bibliographic Information

The influence of BIBW22BS, a dipyridamole derivative, on the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in vitro and in human tumor xenografts. Jansen, W. J. M.; Pinedo, H. M.; Van Der Wilt, C. L.; Feller, N.; Bamberger, U.; Boven, E. Department Medical Oncology, Amsterdam, Neth. European Journal of Cancer, Part A (1995), 31A(13/14), 2313-19. Publisher: Elsevier, CODEN: EJCTEA Journal written in English. CAN 124:249952 AN 1996:139911 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Dipyridamole is known as a potent inhibitor of facilitated diffusion-mediated nucleoside transport as well as a modulator of "classical" multidrug resistance. BIBW22BS, a deriv. of dipyridamole, has been found to be 20- to 100-fold more potent in the reversal of multidrug resistance when compared to the parent compd. In parallel, we studied the efficacy of BIBW22BS in the modulation of the antiproliferative effects of 5-fluorouracil, methotrexate and gemcitabine in human cancer cell lines. BIBW22BS, at non-toxic concns. up to 1.0 μM, increased the antiproliferative effects of 5-fluorouracil 2- to 6-fold in seven of the eight colon cancer cell lines tested in a dose-dependent manner. The addn. of 1.0 μM BIBW22BS to methotrexate resulted in a slight increase in the antiproliferative effects, but inhibited the activity of gemcitabine 30- to 100-fold in various cancer cell lines. In vitro, no notable difference was found between BIBW22BS and dipyridamole in their capacity to modulate the activity of the antimetabolites studied. BIBW22BS did not affect the growth inhibition induced by 5-fluorouracil or gemcitabine in human tumor xenografts grown s.c. in nude mice. We confirmed the higher potency of BIBW22BS when compared to dipyridamole in the reversal of drug resistance in the Pgp-pos. COLO 320 cell line.

Answer 89:

Bibliographic Information

Intratumoral chemotherapy with a sustained-release drug delivery system inhibits growth of human pancreatic cancer xenografts. Smith, Jill P.; Stock, Elizabeth; Orenberg, Elaine K.; Yu, Ning Y.; Kanekal, Sarathchandra; Brown, Dennis M. Dep. Medicine, Pennsylvania State Univ., Hershey, PA, USA. Anti-Cancer Drugs (1995), 6(6), 717-26. Publisher: Rapid Science Publishers, CODEN: ANTDEV ISSN: 0959-4973. Journal written in English. CAN 124:135020 AN 1996:49697 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

This study provides the first evidence that treatment of human pancreatic adenocarcinoma is markedly improved by the intratumoral administration of chemotherapeutic agents in a novel drug delivery system. The effect of chemotherapeutic agents delivered in a sustained-release, protein-based, injectable gel was evaluated on the growth of human pancreatic adenocarcinoma cell line, BxPC-3. In vitro chemosensitivity of BxPC-3 cells exposed for 24 or 72 h to fluorouracil (0.01-5 mM), cisplatin or doxorubicin (0.1-50 μM) and floxuridine, vinblastine, mitomycin or paclitaxel (1.0-100 μM) was compared with that of untreated cells. In vitro chemosensitivity was also studied with fluorouracil and mitomycin in the poorly differentiated PANC-1, human pancreatic cancer cell line. Survival was detd. after 7-10 days. All drugs decreased cell growth in a dose dependent fashion. The efficacy of fluorouracil, cisplatin and doxorubicin increased with prolonged exposure, rendering these drugs most appropriate for a sustained-release prepn. For in vivo studies, athymic nude mice bearing BxPC-3 xenografts were treated either with fluorouracil, cisplatin or doxorubicin in the therapeutic injectable gel contg. epinephrine or with vehicle alone administered intratumorally on days 1 and 4. After 28 days, the mice were sacrificed and tumors dissected and weighed. Tumors in mice treated with the injectable gel decreased in size by 72-79% compared with tumors in untreated controls and tumors treated with vehicle alone. Intratumoral injection of drug soln. and i.p. injection of drug in the injectable gel did not change tumor size compared with controls. In a drug-retention study, mice were injected intratumorally with [3H]fluorouracil either in the injectable gel or in soln. Sustained radioactivity was obsd. in tumors injected with the gel, and, conversely, greater radioactivity was detected in the liver and kidneys in mice receiving the radiolabeled soln.

These results suggest that the therapeutic injectable gel chemotherapy, when given intratumorally, may improve tumor response with less systemic toxicity in comparison with conventional systemic chemotherapy.

Answer 90:

Bibliographic Information

Recombinant human interferon alpha-2a increases the antitumor activity of 5-fluorouracil on human colon carcinoma xenograft Co-4 without any change in 5-FU pharmacokinetics. Kase, Suguru; Kubota, Tetsuro; Watanabe, Masahiko; Furukawa, Toshiharu; Tanino, Hirokazu; Kuo, Tsong-Hong; Saikawa, Yoshiro; Teramoto, Tatsuo; Kitajima, Masaki. School Medicine, Keio University, Tokyo, Japan. Anticancer Research (1995), 15(1), 153-6. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 123:81309 AN 1995:625455 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors investigated the modulating effect of recombinant human interferon α-2a (IFN-α) on the antitumor activity of 5-fluorouracil (5-FU) against a human colon carcinoma xenograft (Co-4) in nude mice with ref. to changes in the pharmacokinetic pattern of 5-FU. Mice bearing Co-4 received 5-FU i.p. at a dose of 90 mg/kg once with or without IFN-α, which was administered s.c. at a dose of 60.000 IU/mouse daily for 7 days before 5-FU treatment. When the area under the curve and peak plasma concn. of 5-FU with or without IFN-α were measured as pharmacokinetic parameters, the pharmacokinetics of 5-FU was not changed by IFN-α administration. Apparently, the modulating effect of IFN-α on 5-FU does not involve augmentation of 5-FU pharmacokinetic parameters.

Answer 91:

Bibliographic Information

Predictability of clinical response to anticancer agents in human cancer xenografts. Tsukamoto, Fumine. Med. Sch., Osaka Univ., Suita, Japan. Osaka Daigaku Igaku Zasshi (1994), 46(4), 251-61. CODEN: ODIZAK ISSN: 0369-710X. Journal written in Japanese. CAN 121:124753 AN 1994:524753 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Nude mouse transplanted human tumors retained original sensitivity to antitumor drugs, and was useful in secondary screening for the sensitivity to tumor chemotherapy. Fresh tumor tissues were transplanted and maintained in nude mice in 77 cases (tried: 247 cases), and sensitivity of the transplanted tumors to chemotherapy was compared between human therapy and in nude mice using regimen

used clin. in 17 cases with 21 expts. (stomach, breast, colon, pancreas, esophagus. melanoma). Tested drugs were adriamycin, cisplatin, cyclophosphamide, cytarabine, dacarbazine, doxifluoridine, epirubicin, 5-fluorouracil, M-83 (a mitomycin C deriv.), mitomycin C, tegafur, and UFT. Chemotherapy in nude mice was effective in 6 expts., which coincided with clin. results in 5 cases. The ineffective 15 cases in nude mice coincided with the clin. results in all cases.

Answer 92:

Bibliographic Information

Combined radioimmunotherapy and chemotherapy of human colon carcinoma grafted in nude mice, advantages and limitations. Chalandon, Yves; Mach, Jean-Pierre; Pelegrin, Andre; Folli, Silvio; Buchegger, Franz. Inst. Biochem., Univ. Lausanne, Epalinges, Switz. Anticancer Research (1992), 12(4), 1131-39. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 121:30033 AN 1994:430033 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To det. if 5-fluorouracil (5FU) could potentiate the effect of radioimmunotherapy (RIT), nude mice bearing s.c. human colon carcinoma xenografts were treated by 1 or 2 i.v. injection(s) of subtherapeutic doses of 131I-labeled F(ab')2 from anti-carcinoembryonic antigen monoclonal antibodies combined with 5 daily i.p. injections of 5FU. Control mice received either 131I F(ab')2 alone, 5FU alone or no treatment. RIT alone induced significant tumor regression, while 5FU alone gave only minimal tumor growth inhibition. The combined treatment group also resulted in long-term tumor regression with tumors remaining significantly smaller than in the RIT alone group. There was however, no significant difference in tumor recurrence time between the groups treated with RIT alone or with RIT + 5FU. Myelotoxicity, the major side effect of RIT, detected by the decrease of peripheral white blood cells (WBC), was shown to be almost identical between the groups receiving only RIT or only 5FU. Surprisingly, there was no cumulative bone marrow toxicity in animals which received 5FU before RIT. Furthermore, in the latter group, the WBC levels after RIT were significantly higher than in the control group receiving only RIT. Taken together, the results demonstrate the higher therapeutic efficiency of RIT as compared to 5FU in this model. They do not show, however, that the combination of the two forms of treatment can induce longer tumor remission. Interestingly, the WBC results suggest that 5FU given before RIT can have a radioprotective effect on bone marrow, possibly by selecting radioresistant bone marrow stem cells.

Answer 93:

Bibliographic Information

The role of additional chemotherapy with oral UFT in intravenous combination chemotherapy with cisplatin and 5-fluorouracil for human gastric cancer xenograft lines of well- and poorly- differentiated adenocarcinomas transplanted in nude mice. Tseng, Chen-Chiu; Nio, Yoshinori; Tsubono, Michihiko; Kawabata, Kazuya; Masai, Yoshikazu; Hayashi, Hitoshi; Fukumoto, Manabu; Tobe, Takayoshi. First Dep. Surg., Kyoto Univ. Fac. Med., Kyoto, Japan. Anticancer Research (1992), 12(4), 1295-9. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 121:26395 AN 1994:426395 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In order to assess the role of maintenance chemotherapy with the oral anticancer agent UFT, a mixt. of uracil and futraful, in the intensive i.v. chemotherapy for gastric cancer, nude mice transplanted with human gastric cancer xenografts were treated with i.v. 5-fluorouracil (5-FU) and cisplatin (CDDP), alone or in combination, with or without the oral anticancer agent UFT. UFT was given at its maximal clin. dose of 10 mg/kg of body wt. daily for 2 wk, while 5-FU and/or CDDP was i.v. administered at the dose of 20 mg/kg and 1.8 mg/kg of body wt. resp. once a week, alone or in combination, for two weeks. The results revealed that 5-FU or CDDP alone were ineffective for both GC-YN, a well differentiated adenocarcinoma line, and GC-SF, a poorly differentiated adenocarcinoma line; however, UFT was effective for GC-SF. In combinations, only the three - agent combination 5-FU+CDDP+UFT (FPU) was effective for GC-YN; however, all the two - agent combinations and FPU were effective for GC-SF. FPU significantly suppressed the growth of GC-YN much more than all the other treatment groups. In contrast, although all combinations as well as UFT alone were effective for GC-SF, there was no significant difference among these effective groups. Moreover, no side effects were noted in combined use of

UFT. This study suggests that oral UFT as a maintenance treatment may be beneficial in the combination chemotherapy for human gastric cancer.

Answer 94:

Bibliographic Information

Similarity of serum - tumor pharmacokinetics of antitumor agents in man and nude mice. Kubota, Tetsuro; Inoue, So; Furukawa, Toshihuaru; Ishibiki, Kyuya; Kitajima, Masaki; Kawamura, Eiji; Hoffman, Robert M. Sch. Med., Keio Univ., Tokyo, Japan. Anticancer Research (1993), 13(5A), 1481-4. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 120:315103 AN 1994:315103 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A pharmacokinetic comparison was made between nude mice and human gastric cancer patients. This comparison is important in order to optimize the human tumor xenograft - nude mouse system as a screening panel for potential antitumor agents. In this report, mitomycin C (MMC), doxorubicin (DXR), 5-fluorouracil (5-FU) and cisplatin (DDP) were administered to nude mice bearing human tumor s.c. xenografts in max. tolerated doses and to patients with gastric cancer at conventional doses. The concns. of antitumor agents in serum and tumor were detected by bioassay for MMC and 5-FU, by high performance liq. chromatog. for DXR, and by at. absorption method for DDP. Peak drug concns. in the serum (Cmax) of mice and humans correlated well with statistical significance (R = 0.999, P<0.0001). When Cmax and drug concns. in the tumor (T) of mice and human were compared with each other to evaluate the uptake of drugs into the tumor from the serum and calcd. as T/Cmax, similar results were obsd. for the same agent with statistical significance (r = 0.990, p<0.02). These results indicate that the human tumor xenograft - nude mouse system and humans are essentially similar pharmacodynamically, which further validates the use of this system to evaluate potential antitumor agents.

Answer 95:

Bibliographic Information

Combination versus single agent therapy in effecting complete therapeutic response in human bladder cancer: analysis of cisplatin and/or 5-fluorouracil in an in vivo survival model. Keane, Thomas E.; Gingrich, Jeffrey R.; Rosner, G.; Webb, Karen S.; Poulton, Susan H.; Walther, Philip J. Sch. Med., Duke Univ., Durham, NC, USA. Cancer Research (1994), 54(2), 475-81. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 120:153212 AN 1994:153212 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

An in vivo study of cisplatin (CDDP) and 5-fluorouracil (5FU) cytotoxicity was performed using a multidose matrix with a human bladder transitional cell carcinoma xenograft tumor line (DU4284) tested by subrenal capsule assay in 154 nude mice (NM-SRCA). Statistical anal. of initial growth inhibition at 20 days and host survival demonstrates therapeutic, cooperative interaction. Toxic doses of either CDDP or 5FU alone as well as low-dose combinations provided modest or no survival benefit. The single dose of CDDP (7 mg/kg) and of 5FU (100 mg/kg) was best (by anal. of efficacy and toxicity) of those tested and caused >97% initial regression. While 94% of controls incurred tumor deaths by 225 days, 75% treated at this dose were tumor free and likely cured. The authors' conclusions were: (a) NM-SRCA human xenograft testing is excellent for rapid in vivo screening of promising treatment strategies to evaluate for efficacy at acceptable toxicity, but confirmation of true therapeutic impact should be sought by correlating initial growth inhibition with host survival; (b) enhanced survival seen only when CDDP/5FU are used together (vs. either single agent) supports the value of pursuing histiotype-specific screening of potentially synergistic drug combinations; and (c) of clin. relevance, human transitional cell carcinoma is now identified as a histiotype in which a therapeutic, cooperative interaction between CDDP/5FU has been demonstrated in vivo.

Answer 96:

Bibliographic Information

The modulation by L-leucovorin of 5-fluorouracil antitumor activity on human colon carcinoma cells in vitro and in vivo. Kase, Suguru; Kubota, Tetsuro; Watanabe, Masahiko; Takahara, Tetsuya; Takeuchi, Tooru; Yamaguchi, Hiroshi; Furukawa, Toshiharu; Teramoto, Tatsuo; Kodaira, Susumu; et al. Sch. Med., Keio Univ., Tokyo, Japan. Surgery Today (1993), 23(7), 615-20. CODEN: SUTOE5 ISSN: 0941-1291. Journal written in English. CAN 120:180 AN 1994:180 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors investigated the modulating effect of L-leucovorin (LV) on the antitumor effect of 5-fluorouracil (5-FU) against human colon carcinoma cells (C-1) in vitro and human colon carcinoma xenografts (Co-4) in nude mice. The modulating effect of LV on 5-FU reached an optimal concn. of 40 - 80 μg/mL in vitro which was detected by a colorimetric MTT assay. An optimal dose of 200 mg/kg was also obsd. in the nude mouse system. The modulating effect of LV increased according to the increment of thymidylate synthetase inhibition in vivo. Since the pharmacokinetic pattern of LV in the nude mice administered LV at 200 mg/kg was similar to that in patients treated with LV at a dose of 100 mg/m2, this clin. method of administration was thought to be adequate for modulating the antitumor activity of 5-FU against clin. colon carcinomas.

Answer 97:

Bibliographic Information

Use of poly(ortho esters) in the controlled release of therapeutic agents. Heller, J.; Roskos, K. V.; Duncan, R. Controlled Release Biomed. Polym. Dep., SRI Int., Menlo Park, CA, USA. Makromolekulare Chemie, Macromolecular Symposia (1993), 70-71(34th International Symposium on Macromolecules, 1992), 163-71. CODEN: MCMSES ISSN: 0258-0322. Journal written in English. CAN 119:233837 AN 1993:633837 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Poly(ortho esters) have been under development since 1970 and are the first polymer system that has been specifically designed for drug delivery applications. At this time, three distinctly different families of polymers have been described. One family is prepd. by a transesterification reaction between diethoxytetrahydrofuran and a diol, another family is prepd. by the reaction of polyols with diketene acetals and the third family is prepd. by a transesterification reaction between a triol and an alkyl orthoacetate. The use of these polymers in drug delivery applications is illustrated with 5-fluorouracil devices used in the treatment of human colorectal cancer xenografted in nude mice and with the delayed release of lysozyme, used as a model protein.

Answer 98:

Bibliographic Information

Antitumor activity of BOF-A2, a new 5-fluorouracil derivative, against human cancers xenografted in nude mice by intermittent administration. Fujita, Fumiko; Fujita, Masahide; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1993), 20(2), 223-8. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 119:425 AN 1993:400425 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor effects of BOF-A 2 given intermittently was evaluated with human gastric (H-111, H-83), colorectal (H-110, H-143) and lung (H-74, LC-376) cancers xenografted in nude mice and compared with those by continuous administration. BOF-A 2 was orally given 3 or 4 times per wk at 30 or 35 mg/kg over 4 wk. This drug was effective to 5 strains except H-110 (IR ≥ 80 %) and caused tumor regression in mice bearing H-81 esp. Moreover, the drug was effective to H-74 which is rather insensitive to 5-FU and its known

derivs. When the drug was given orally to nude mice xenografted with LC-376, 5-FU levels in the tumor tissue was lasted for a long time as compared to UFT. It would be concluded that BOF-A 2 was much effective to insensitive tumor to fluorinated pyrimidines or other anticancers, because of persistence of high levels of 5-FU in the tumor tissue. On the other hand, diarrhea which is caused by other fluorinated pyrimidines or consecutive administration of BOF-A2, was mild by the intermittent administration of BOF-A2.

Answer 99:

Bibliographic Information

Antitumor activity of combination treatment of BOF-A2 with CDDP against human lung cancers xenografted in nude mice. Fujita, Fumiko; Fujita, Masahide; Sakamoto, Yasuo; Taguchi, Tetsuo. Exp. Cancer Chemother. Res. Lab., Co., Ltd., Osaka, Japan. Gan to Kagaku Ryoho (1993), 20(2), 215-21. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 119:424 AN 1993:400424 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

CDDP, commonly used in cancer chemotherapy, behaves as not only effector but also modulator of 5-FU when combined with 5-FU and its derivs. Therefore, the antitumor activity of combination treatment of BOF-A2, a new 5-fluorouracil deriv., with CDDP was evaluated with two human lung cancers (H-74 and LC-376) xenografted in nude mice. BOF-A2 was orally administered at 30 mg/kg (MTD) or 15 mg/kg (1/2 MTD) 3 times a week totally twelve times, and CDDP was administered i.p. at 5 mg/kg (MTD) or 2.5 mg/kg (1/2 MTD) once a week totally 4 times. The antitumor effect of combination of two drugs at the 1/2 MTD was effective to H-74 and markedly effective to LC-376, and the effect was more remarkable than each drug administered individually at the 1/2 MTD, and the combination effect was additive. The effect by the combination was not synergistic but showed a similar activity compared with single drug given individually at the MTD. Moreover, the side effect of combination of the 1/2 MTD was less than group given MTD of CDDP in terms of body wt. loss. These data suggests a clin. usefulness of combination BOF-A2 with CDDP against lung cancer.

Answer 100:

Bibliographic Information

Modulation by l-leucovorin of 1-hexylcarbamoyl-5-fluorouracil antitumor activity on human gastric and colon carcinomas serially transplanted into nude mice. Kubota, Tetsuro; Kase, Suguru; Furukawa, Toshiharu; Tanino, Hirokazu; Kuo, Tsong Hong; Saikawa, Yoshiro; Nishibori, Hideki; Ishibiki, Kyuya; Kitajima, Masaki; et al. Sch. Med., Keio Univ., Tokyo, Japan. Anticancer Research (1992), 12(5), 1549-53. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 118:52020 AN 1993:52020 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Exptl. biochem. modulation of 1-hexylcarbamoyl-5-fluorouracil (HCFU) with l-leucovorin (LV) was carried out using human gastric (H-111) and colon (Co-4) carcinoma xenografts serially transplanted into nude mice. Thirty-five or 70 mg/kg HCFU dissolved in 0.2 mL of 1% hydroxymethyl cellulose was administered orally daily for 3 wk except Sundays, and 50, 100, 200 or 300 mg/kg LV dissolved in 0.2 mL physiol. saline was administered po 30 min before administration of HCFU. The biochem. modulated antitumor activity was evaluated in terms of actual tumor wt., the relative mean tumor wt. and the degree of inhibition of thymidylate synthetase (TS) in the tumors at the end of the expts. Although 35 mg/kg HCFU was ineffective against gastric carcinoma H-111, combination with 200 or 300 mg/kg LV resulted in a pos. antitumor effect of HCFU on this strain without any increase of side effects in terms of body wt. loss and mouse mortality. The colon carcinoma strain Co-4 showed marginal sensitivity to HCFU (35 mg/kg) alone, but 50 or 100 mg/kg LV modulated the antitumor activity of HCFU on Co-4 to produce a significant pos. effect without any increase in toxicity, and HCFU administered with 100 mg/kg LV was more effective than the max. tolerated dose of HCFU (70 mg/kg) alone. The TS inhibition rate was closely related to the biochem. modulation of HCFU antitumor activity by LV, suggesting that the modulation involves an increase of the ternary complex of TS, 5,10-methylene tetrahydrofolate from LV and 5-fluorodeoxyuridine 5'-monophosphate (FdUMP). Combination of HCFU and LV is therefore thought to be useful in increasing the antitumor activity of HCFU on gastrointestinal carcinomas without enhancing its toxicity.

Answer 101:

Bibliographic Information

Levamisole plus 5-fluorouracil inhibits the growth of human colorectal xenografts in nude mice. Van Ginckel, Robert; Distelmans, Wim; De Bradander, Marc; Callens, Myriam; Janssens, Boudewijn; Jagers, Els; Wouters, Luc; De Coster, Roland; Janssen, Paul A. J. Janssen Res. Found., Beerse, Belg. Eur. J. Cancer, Part A (1992), 28A(6-7), 1137-9. CODEN: EJCTEA Journal written in English. CAN 117:184434 AN 1992:584434 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fragments of human colorectal adenocarcinomas were inserted under the renal capsule of nude mice. The growth of these tumor grafts was inhibited by the combination of 5-fluorouracil (5-FU) and levamisole. An alternating regimen of 2.5 kg levamisole/kg and 20 mg 5-FU/kg decreased the size of tumor implants by 33-59% and/or increased the no. of macroscopically disappeared fragments in the combined treatment group compared with ineffective monotherapy with saline, levamisole, or 5-FU. This model could be valuable for investigating the mechanism of action of levamisole and for evaluating the effects of this adjuvant therapy in other oncol. settings.

Answer 102:

Bibliographic Information

Modulation by recombinant α-2A-interferon the activity and mechanism of action of 5-fluorouracil on xenografted human colon cancer in nude mice: preliminary report. Yoshida, Kazuhiko; Fujikawa, Toru; Tanabe, Akihiro; Sakurai, Kenji. Sch. Med., Jikei Univ., Tokyo, Japan. Nippon Geka Gakkai Zasshi (1992), 93(5), 559. CODEN: NGGZAK ISSN: 0301-4894. Journal written in Japanese. CAN 117:142964 AN 1992:542964 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anticancer activity of 5-fluorouracil (5-FU) can be potentiated by recombinant α-2A interferon (γINFα-2a). The effects of γINFα-2a on intratumor levels of 5-FU, 5-fluorodeoxyuridylate (5-FdUMP), and thymidylate synthase were studied to elucidate the modulation mechanism of γINFα-2a. The intratumor levels of 5-FU and 5-FdUMP in xenografted human colon cancer in nude mice were not changed by the combination of γINFα-2a. However, the free and total thymidylate synthase (TS) in tumor tissue was significantly increased. The increase in total TS indicated an increase of 5-FdUMP binding to TS, and the increase in free TS may suggest the existence of 5-FU resistance.

Answer 103:

Bibliographic Information

A new type of antitumor substances, polyoxomolybdates. Fujita, Haruhisa; Fujita, Tomonobu; Sakurai, Toshiharu; Seto, Yoshiko. Sch. Med., Keio Univ., Tokyo, Japan. Chemotherapy (Tokyo) (1992), 40(2), 173-8. CODEN: NKRZAZ ISSN: 0009-3165. Journal written in English. CAN 117:375 AN 1992:400375 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The growth suppressions of [NH3CHMe2]6[Mo7O24].3H2O (PM-8) against Co-4, human colon cancer, xenografted under the renal capsule in cd-1 mice were equal or superior to that of 5-fluorouracil, mitomycin C, 1-(4-amino-2-methylpyrimidine-5-yl)methyl-3-(2-chloroethyl)-3-nitrosourea HCl, adriamycin, and cis-Pt diammine dichloride. Potent antitumor activity of PM-8 was also established against MX-1, human breast cancer, and OAT, human lung cancer, xenografted in athymic nude mice. Antitumor activities of other polyoxomolybdates are also described.

Answer 104:

Bibliographic Information

Comparative studies on the antitumor activity of fluorinated pyrimidine derivatives against human bladder, cervical and ovarian cancer xenografts in nude mice. Miwa, Masanori; Sekiguchi, Fumiko; Akaza, Hideyuki; Tokita, Hisashi; Nitta, Kazuo; Adachi, Shigemi; Kanazawa, Kohji; Ishitsuka, Hideo. Dep. Oncol. Immunol., Nippon Roche Res. Cent., Kamakura, Japan. Gan to Kagaku Ryoho (1991), 18(10), 1579-86. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 116:333 AN 1992:333 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Fluorinated pyrimidines given orally were examd. for their antitumor activity with 11 human cancer xenograft models (4 bladder, 4 cervical and 3 ovarian cancers). The drugs were evaluated to be effective when they inhibited tumor growth over 58%. UFT was not effective against the 11 cancer xenografts tested. 5-Fluorouracil (5-FU) was effective against only 1 bladder cancer xenograft among 6 cancer xenografts tested. On the other hand, 5'-deoxy-5-fluorouridine (5'-DFUR) was effective against 1 bladder, 3 cervical and 1 ovarian cancer xenografts. The antitumor activity of 5'-DFUR was correlated with the enzyme activity of pyrimidine nucleoside phosphorylase, which is an essential enzyme for phosphorolysis of 5'-DFUR to 5-FU.

Answer 105:

Bibliographic Information

In vivo inhibitory effect of anticancer agents on human pancreatic cancer xenografts transplanted in nude mice. Imai, Shiro; Nio, Yoshinori; Shiraishi, Takahiro; Manabe, Tadao; Tobe, Takayoshi. Fac. Med., Kyoto Univ., Kyoto, Japan. Anticancer Research (1991), 11(2), 657-64. CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 115:174179 AN 1991:574179 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Pancreatic cancer is one of the neoplasms resistant to chemotherapy. In the present study human pancreatic cancer xenografts (3 adenocarcinomas and 1 cystoadenocarcinoma) were s.c. transplanted in nude mice and after the tumors grew to 100-300 mm3, the mice were i.p. administered with mitomycin C (MMC), adriamycin (ADR), 5-fluorouracil (5-FU), carboquone (CQ), cisplatinum (CDDP), nimustine chloride (ACNU) or DWA2114R at 1/3 LD50 on days 0, 4, and 8. The tumor sizes on day 12 were compared with those on day 0. MMC and CQ significantly inhibited the tumor growth of 3 lines, and ACNU, CDDP and ADR inhibited the growth of 1 line. Further, 5-FU, futrafur, carmofur, UFT, and L-phenylalanine mustard (L-PAM) were orally administered to mice into which 1 adenocarcinoma line had been transplanted. While none of fluoropyrimidines inhibited tumor growth, L-PAM at 4 mg/kg significantly inhibited growth, although it was accompanied by severe body wt. loss. In the present study several agents significantly inhibited tumor growth, but none of them could induce the regression of the tumor when used singly. These results suggest that CQ, ACNU, CDDP and L-PAM may be applied to the chemotherapy of pancreatic cancer. However, the effect of a single agent is restricted and the development of new combination treatments is urgently required.

Answer 106:

Bibliographic Information

Inhibitory effect of bleomycin A6 on human colon cancer xenografts in nude mice. Deng, Yongchuan; Zhen, Yongsu; Zheng, Shu; Xue, Yuchuan. Inst. Med. Biotechnol., Chin. Acad. Sci., Beijing, Peop. Rep. China. Zhongguo Yixue Kexueyuan Xuebao (1990), 12(5), 335-40. CODEN: CIHPDR ISSN: 1000-503X. Journal written in Chinese. CAN 115:149850 AN 1991:549850 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Bleomycin A6 was found to be highly active against established human cancer cell lines derived from colon cancer (HT-29) and cecum cancer (Hce-8693), as evaluated by clonogenic assay. These human cancer cells were serially transplanted in nude mice. At a tolerable dosage level, bleomycin A6 exerted remarkable growth inhibition on human colon cancer HT-29 and cecum cancer Hce-8693 xenografts (approx. 90% inhibition). No histopathol. changes were found in the organs of treated animals. Compared on the basis of equitoxic doses (1/9 LD50), bleomycin A6 exerted much stronger growth inhibition against colon cancer HT-29 xenografts in nude mice than 5-fluorouracil and mitomycin C, with inhibition rates of 82%, 12% and 53%, resp. More extensive necrosis was found in tumors treated with bleomycin A6 than in those treated with mitomycin C or 5-fluorouracil. The ratio values of non-necrotic tumor tissue to whole tumor tissue for bleomycin A6, mitomycin C, and 5-fluorouracil were 0.33, 0.65, and 0.57, resp. These observations indicate that bleomycin A6 is a potent antitumor agent against colon cancer xenografts and may be useful in human colon cancer chemotherapy.

Answer 107:

Bibliographic Information

Studies on chemotherapy for adenocarcinoma of the uterine cervix using xenografts transplanted in nude mice. Yamagishi, Masaji. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. Nippon Sanka Fujinka Gakkai Zasshi (1991), 43(2), 165-72. CODEN: NISFAY ISSN: 0300-9165. Journal written in Japanese. CAN 115:341 AN 1991:400341 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adenocarcinoma of the human uterine cervix was successively transplanted into nude mice and the effects of chemotherapy on adenocarcinoma of uterine cervix were investigated in this transplanted tumor. First, it was confirmed that both the original tumor and the transplanted tumor were apparently histol. the same as adenocarcinoma of the uterine cervix (endocervical type). And the transplanted tumor was shown to have the features of adenocarcinoma by an electron microscope. The doubleing time of the transplanted tumor was 9.2 days. For the chemotherapy study, first the therapeutic effects of 11 kinds of agents were screened by single-agent chemotherapy applied to the transplanted tumor. From the results of this series, 6 regimens for multi-agent chemotherapy were tried on the transplanted tumor. The effects of the chemotherapy were evaluated following Battelle Columbus Labs. Protocol and histopathol. The relative regression rates for the tumors treated with mitomycin C (MMC) + cyclophosphamide (CPM) and MMC + CPM + methotrexate (MTX) were 72.99 and 80.9% (Tn/To = 0.84), resp. The results suggest that the combinations of MMC + CPM or MMC + CPM + MTX are regimens that are possibly effective on the adenocarcinoma of human uterine cervix and are worth be trying clin.

Answer 108:

Bibliographic Information

Comparative study of antitumor agents in serum and tumor between nude mouse and human. Inoue, So. Sch. Med., Keio Univ., Tokyo, Japan. Keio Igaku (1991), 68(1), 57-65. CODEN: KEIGAS ISSN: 0368-5179. Journal written in Japanese. CAN 115:188 AN 1991:400188 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The pharmacokinetic comparison between nude mouse and human beings is important to using the human tumor xenograft-nude mouse system as a screening panel for newly developed antitumor agents. Mitomycin C, adriamycin, 5-fluorouracil, cisplatin, and the platinum-related compds. (carboplatin and DWA2114R) were administered to nude mice bearing human tumor xenografts in max. tolerated doses and to patients with cancer in conventionally available doses in clinics. The concns. of antitumor agents in serum and tumor were detected by bioassay, HPLC, and the at. absorption method. The max. serum concn. (Cmax) in μg/mL and concn. in tumor (T) in μg/g in nude mouse and human were compared to each other and the shift of drugs from serum to tumor was calcd. as

T/Cmax. Although the different doses of the agents were administered in nude mice and humans, the T/Cmax ratios were similar to each other.

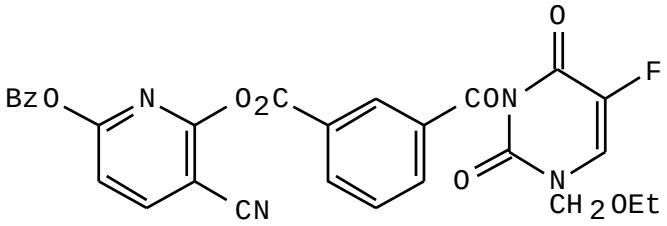
Answer 109:

Bibliographic Information

Antitumor activity and metabolism of BOF-A2, a new 5-fluorouracil derivative, with human cancers xenografted in nude mice. Shirasaka, Tetsuhiko; Fujita, Fumiko; Fujita, Masahide; Fukushima, Masakazu; Taguchi, Tetsuo; Fujii, Setsuro. Biwako Res. Inst., Otsuka Pharm. Co., Ltd., Japan. Gan to Kagaku Ryoho (1990), 17(9), 1871-6. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 114:199159 AN 1991:199159 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor activity of BOF-A2 (I), a new 5-fluorouracil (5-FU) deriv., was evaluated with human gastric (H-111 and H-81), colorectal (H-143), pancreatic (H-48) and breast (H-31) cancer cells grafted in nude mice. Twenty-five daily oral doses of BOF-A2 at 17.5 30 mg/kg caused a marked inhibition or regression of H-81, H-143, and H-31 cancers. BOF-A2 affected also H-111 and H-48 cells which have low sensitivity to 5-FU and its derivs. Mice tolerated BOF-A2 without severe toxicity. When BOF-A2 was given orally, 5-FU levels in the blood persisted for a longer time as compared to 5-FU and UFT. Furthermore, 5-FU levels in the tumor tissue were higher and persisted much longer than those in the blood. This maintenance and persistence of 5-FU levels in the blood can produce high antitumor effects of BOF-A2 against human cancers xenografted in nude mice.



I

Answer 110:

Bibliographic Information

Evaluation of predictability of in vitro SDI assay in comparison with in vivo nude mouse assay. Fujita, Masahide; Tanigawa, Keiko; Fujita, Fumiko; Sakamoto, Yasuo; Shimozuma, Kojiro; Kusuyama, Takatsugu; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1989), 16(10), 3435-41. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 112:69560 AN 1990:69560 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Twenty lines of human gastro-intestinal and breast cancer xenografts, in which chemosensitivity spectra by the in vivo nude mouse assay had been clarified, were subjected to the in vitro SDI (succinate dehydrogenase inhibition) assay using MTT dye to assess the accuracy of this drug sensitivity test against 4 drugs, i.e., mitomycin C (MMC), adriamycin (ADM), 5-fluorouracil (5-FU), and cisplatin (CDDP). After 3 days incubation, the suspension of tumor cells showed a marked decrease of SD activity even when no anticancer drug was added to the assay medium. Among these 4 drugs evaluated, MMC exhibited a statistically significant correlation between chemosensitivity values of the in vitro SDI assay and those of the nude mouse assay. However, the other 3 drugs demonstrated no correlation between the values of these two methods. Since the primary cultured fibroblasts revealed, in general, lower sensitivity to these drugs, contamination of fibroblast may decrease the SDI values when materials from solid tumors with rich stroma such as a type of stomach cancer were subjected. It is considered that the prediction of chemosensitivity to every drugs will be impossible by an in vitro SDI assay.

Answer 111:

Bibliographic Information

Selectivity of CF and 5-fluorouracil: critical role of polyglutamylation. Houghton, Janet A.; Williams, Larry G.; DeGraaf, Siebold S. N.; Radparvar, Saeed; Wainer, Irving W.; Rodman, John R.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Advances in Experimental Medicine and Biology (1988), 244(Expanding Role Folates Fluoropyrimidines Cancer Chemother.), 85-95. CODEN: AEMBAP ISSN: 0065-2598. Journal written in English. CAN 111:33192 AN 1989:433192 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Data are given on the inhibition by 5-fluorouracil of thymidylate synthase in human color adenocarcinoma xenografts in mice, as well as on the concn. and distribution on the polyglutamylated forms of 5,10-methylenetetrahydrofolate and tetrahydrofolate (CH2-H4PteGlunand H4PteGlun, resp.) in the tumors and the formation and stability of the fluorodeoxyuridine monophosphate (FdUMP)-thymidylate synthase (TS)-CH2-H4PteGlu complex. In addn., the xenograft models were used to examine the modulation of CH2-H4PteGlun and H4PteGlun pools in the tumors relative to the levels of the active isomer (6S) of 5-formyltetrahydrofolate (citrovorum factor; CF) when the host mice were infused with (6R,S)-CF at different rates. It is suggested that the duration of elevation of reduced folate pools is detd. by the length of the (6E,S)-CF infusion and that the duration of administration of (6R,S)-CF should be prolonged, at least beyond i.v. bolus injection, to allow the longer-polyglutamate-chain forms of CH2-H4PteGlu and H4PteGlu to be synthesized for optimization of the interaction between FdUMP, TS and CH2H4 PteGlu.

Answer 112:

Bibliographic Information

Effects of 5-FU and cis-DDP combination on human colorectal tumor xenografts. Pratesi, Graziella; Manzotti, Carla; Tortoreto, Monica; Prosperi, Ennio; Zunino, Franco. Div. Exp. Oncol. B, Ist. Naz. Stud. Cura Tumori, Milan, Italy. Tumori (1989), 75(1), 60-5. CODEN: TUMOAB ISSN: 0300-8916. Journal written in English. CAN 111:356 AN 1989:400356 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect against primary or metastatic human colorectal carcinoma xenografted in nude mice was better with cis-DDP (cisplatin) plus 5-Fu (5-fluorouracil) given i.v. at 24-h intervals than with either drug alone; lower drug doses were tolerated by using cisplatin-5-FU sequence.

Answer 113:

Bibliographic Information

Combined effects of interferon α-A/D with fluoropyrimidine derivatives in subrenal capsule assay. Nishiyama, Masahiko; Takagami, Shinichi; Kirihara, Yoshimasa; Saeki, Toshiaki; Niimi, Ken; Kim, Ryungsa; Jinushi, Kazuto; Toge, Tetsuya; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1988), 15(8), 2285-90. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 109:204561 AN 1988:604561 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Synergistic, additive, or subadditive antitumor effects were obsd. following the combined administration of interferon α-A/D with fluoropyrimidine derivs. (i.e., 5-FU, tegafur, and 5'-deoxy-5-fluorouridine, UFT, and 1-hexylcarbamoyl-5-fluorouracil) to athymic mice

bearing human tumor xenografts (H-111 and SH-10 gastric cancers and CH-5 colon cancer). The combinations were not effective against CH-4 colon cancer of human.

Answer 114:

Bibliographic Information

Combined effects of UFT with other anticancer agents using in vivo chemosensitivity tests. Nishiyama, Masahiko; Niimi, Ken; Takagami, Shinichi; Hirabayashi, Naoki; Yamaguchi, Masahiro; Saeki, Toshiaki; Yoshinaka, Ken; Dian-Chang, Wang; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Japanese Journal of Surgery (1988), 18(1), 93-7. CODEN: JJSGAY ISSN: 0047-1909. Journal written in English. CAN 109:389 AN 1988:400389 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The combined and tumor activity of UFT (tegafur-uracil mixt. 1:4 molar ratio) and other anticancer agents (mitomycin C, 5-fluorouracil, adriamycin, methotrexate, and cis-diamminedichloroplatinum) were studied against 3 human tumor xenografts in a nude mouse exptl. system and in a subrenal capsule assay. The effectiveness of the combination of UFT and mitomycin C was shown in both assays against all tumor xenografts tested.

Answer 115:

Bibliographic Information

Antitumor effect of UFT on human ovarian cancer grafted in nude mice and 5-FU concentration in the tumor and normal tissues. Yoshiya, Norio; Adachi, Shigemi; Misawa, Yoshio; Ishida, Michio; Yuzawa, Hideo; Kanazawa, Koji; Takeuchi, Shoshichi. Sch. Med., Niigata Univ., Niigata, Japan. Gan to Kagaku Ryoho (1988), 15(2), 285-9. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 108:179762 AN 1988:179762 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Antitumor effects of UFT, tegafur (FT-207), cisplatin (CDDP) and the combination of UFT with CDDP were studied in a human ovarian cancer xenograft in nude mice and the concn. of 5-fluorouracil (5-FU) was detd. in the tumor tissue and major organs. UFT (48.6 mg/kg/day) or tegafur (15.0 mg/kg/day) was administered for 20 days, orally, and CDDP (5 mg/kg/day) was administered i.p. each 7th day for 3 wk. The inhibitions of the tumor growths were 49.6% with UFT, -2.3% with tegafur, and 17.7% with CDDP. With the combination of UFT and CDDP, severe side effects were obsd. The concn. of 5-FU in the UFT-treated group was higher than that in the tegafur group: .apprx.2 times in the tumor, 5 times in the liver, 9 times in the kidneys and 4 times in the spleen. The concns of 5-FU in the major organs, esp. in the kidneys, in nude mice that died 10 days after UFT plus CDDP administration were higher than in those of mice receiving only UFT. UFT increases the intratumoral concn. of 5-FU to elicit better antitumor effects and also increases the concn. of 5-FU in various normal organs after long-term administration.

Answer 116:

Bibliographic Information

Sensitivity to antineoplastic agents of squamous cell carcinoma of the uterine cervix xenografted into nude mice. Kawabata, Masakiyo; Hosokawa, Hitoshi; Kato, Kiyoshi; Izumi, Rikuichi. Fac. Med., Toyama Med. Pharm. Univ., Toyama, Japan. Gan to Kagaku Ryoho (1987), 14(11), 3058-63. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 108:68479 AN 1988:68479 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The efficacies of 5 antineoplastic agents (cisplatin, mitomycin, doxorubicin, 5-fluorouracil, and bleomycin) were tested against carcinoma of the human uterine cervix xenografted into nude mice in order to search for effective combination chemotherapy. The responses to cisplatin and mitomycin were the highest. Thus, combination chemotherapies involving cisplatin and mitomycin are recommended for the treatment of squamous cell carcinoma of the uterine cervix.

Answer 117:

Bibliographic Information

Pharmacodynamic aspects of in vitro and in vivo chemosensitivity tests. Isobe, Yo; Kubota, Tetsuro; Asanuma, Fumiki; Kurihara, Hiroaki; Inada, Takao; Fukutomi, Takashi; Ishibiki, Kyuya; Abe, Osahiko. Sch. Med., Keio Univ., Tokyo, Japan. Japanese Journal of Cancer Research (1987), 78(9), 983-90. CODEN: JJCREP ISSN: 0910-5050. Journal written in English. CAN 108:301 AN 1988:301 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To det. the optimal conditions for clonogenic assay, the antitumor activities of 5-fluorouracil (5-FU) in vitro and in vivo were compared from a pharmacodynamic viewpoint in a human carcinoma xenograft-nude mouse system. In the clonogenic assay, tumor cells were exposed to 5-FU continuously for 2 wk, and the results of the assay were evaluated in terms of colony survival rates (T/C). Tumor-bearing BALB/c male nude mice were treated with 5-FU, and the results were evaluated in terms of the lowest values of relative mean tumor wts. (T/C). To compute the area under the curve (AUC) after administration of 5-FU in vitro and in vivo, agar and serum levels of 5-FU were measured by bioassay. Antitumor activities in terms of T/Cs against a gastric carcinoma strain (H-111) depended highly on the AUCs in vitro and in vivo. The T/C in vitro (z) was correlated with the AUC in vitro (w), $z = 58.4 \times 0.99331w$, and the T/C in vivo (y) was also correlated with the AUC in vivo (x), $y = 52.1 \times 0.88552x$. On the assumption that the T/Cs of these two regression equations were equiv. (y = z), a correlation between w and x was derived. To predict the T/C at the max. tolerated dose of 5-FU in mice, the optimal drug concn. in vitro was calcd. to be 2.7 μg/mL, which also proved to suitable for 7 other carcinoma strains. The exptl. system was thought to be adequate for selecting the optimal drug concn. in the clonogenic assay.

Answer 118:

Bibliographic Information

Experimental studies on heterotransplantation of human squamous cell carcinoma in nude mice and sensitivity test for anticancer agents. Sakamoto, Tomoji. Dent. Coll., Hiroshima Univ., Hiroshima, Japan. Hiroshima Daigaku Shigaku Zasshi (1987), 19(1), 1-13. CODEN: HUDJAN ISSN: 0046-7472. Journal written in Japanese. CAN 107:228638 AN 1987:628638 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The antitumor effect of the chemotherapeutic agents bleomycin, peplomycin, mitomycin C, cisplatin, 5-fluorouracil, and methotrexate against human squamous cell carcinoma was evaluated in nude mice heterotransplanted with the human carcinoma. Results indicated that the sensitivity test for anticancer agents in nude mice is closely related to their clin. effectiveness. The true pos. and neg. antitumor effects of the drugs tested were 60 and 100%, resp.

Answer 119:

Bibliographic Information

Fundamental and clinical investigations on the reinforcement of the effects of combination cancer chemotherapy by flow cytometric analysis of DNA histograms. New attempts at reinforcement of antitumor effects using FCM. Sato, Yasumitsu. Sch. Med., Akita Univ., Japan. Akita Igaku (1986), 13(4), 561-86. CODEN: AKIGDV ISSN: 0386-6106. Journal written in

Japanese. CAN 107:168379 AN 1987:568379 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of cis-diamminedichloroplatinum (CDDP), peplomycin (PEP), mitomycin C (MMC), adriamycin (ADM), etoposide (VP-16), 5-fluorouracil (5-FU), and vindesine (VDS) upon the viability and cell cycle progression of cultured human esophageal cancer cells (TE-2, AE-2), human esophageal (AEN-2), or gastric (TK) tumor xenografts growing in nude mice were measured and compared using flow cytometry (FCM) in order to improve the methods of selecting the individual agents and establish the most effective regimen for combination cancer chemotherapy. Anal. of the influence of chemotherapeutic agents on cell cycle kinetics using FCM appeared to be very important in the development of an effective cancer chemotherapy. Recruitment and partial synchronization were esp. useful in reinforcing the antitumor effects of combination chemotherapy on solid cancers.

Answer 120:

Bibliographic Information

Combination chemotherapy with three or four drugs on human breast and gastrointestinal cancer xenografts in nude mice (II). Fujita, Fumiko; Fujita, Masahide; Sakamoto, Yasuo; Shimozuma, Kojiro; Inaba, Hiizu; Taguchi, Tetsuo. Res. Inst. Microb., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1987), 14(5, Pt. 1), 1252-9. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 107:126597 AN 1987:526597 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Combined applications of 4 drugs, vindesine (VDS), methotrexate (MTX), cisplatin (CDDP) and 5'-DFUR (5'-deoxy-5-fluorouridine) against 3 lines of human breast cancer (H-62, H-31, H-71), and one line each of gastric cancer (H-55) and colon cancer (H-110) xenografted into nude mice were evaluated in comparison with CAF (cyclophosphamide, adriamycin and 5-fluorouracil (5-FU) therapy which is commonly used for breast cancer. Combination therapy with 3 drugs (VDS, CDDP and 5'-DFUR) or 4 drugs (VDS, CDP, MTX and 5'-DFUR) achieved a marked effect with tumor shrinkage in 3 lines of tumors (H-55, H-31 and H-62). Moreover, remarkable effects were shown even in the other 2 lines which were insensitive to every single-agent therapy. A synergistic effect was obtained in 3 of the 5 lines examd. These combination therapies were histol. superior to therapies employing single-drug or CAF therapy. The side effects for combination of these 3 or 4 drugs evaluated by body wt. loss were transient and equiv. to maximal dose of VDS or CDCP.

Answer 121:

Bibliographic Information

Therapeutic effect of 5-aza-2'-deoxycytidine in human head and neck tumor xenografts. Braakhuis, Boudewijn J. M.; Leyva, Albert; Pinedo, Herbert M.; Snow, Gordon B. Dep. Otolaryngol., Free Univ. Hosp., Amsterdam, Neth. Editor(s): Rygaard, Joergen. Immune-Defic. Anim. Biomed. Res., Int. Workshop Immune-Defic. Anim., 5th (1987), Meeting Date 1985, 380-3. Publisher: Karger, Basel, Switz CODEN: 55YNAL Conference written in English. CAN 107:108921 AN 1987:508921 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In nude mice bearing xenografts of human head and neck tumors, 5-aza-5'-deoxycytidine retarded tumor growth, in some cases more effectively than vincristine, methotrexate, bleomycin, or 5-fluorouracil.

Answer 122:

Bibliographic Information

Chemo-sensitive differences of primary, metastatic and recurrent tumors of human colorectal cancer. Yamada, Kazutaka; Takao, Sonshin; Maenohara, Shigeho; Saihara, Tetushi; Yoshinaga, Atsunori; Haruyama, Katsuro; Mitsuda, Kazunobu; Makizumi, Kanro; Ishizawa, Takashi; Shimazu, Hisaaki. Sch. Med., Kagoshima Univ., Kagoshima, Japan. Nippon Shokakibyo Gakkai Zasshi (1986), 83(11), 2318-24. CODEN: NIPAA4 ISSN: 0369-4259. Journal written in Japanese. CAN 106:207311 AN 1987:207311 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Tumor lines xenografts in nude mice used in this study include COK-1 and COK-7. COK-1 (PT, LN and RE) has been established from the primary (PT) lymph node metastatic (LN) and local recurrent (RE) tumors of human colon cancer, and COK-7 (PT and LiM) has been established from the primary(PT) and liver metastatic(LiM) tumors of human rectal cancer. These tumor lines were used for the study of chemotherapeutic responses to such anti-cancer drugs as 5-fluorouracil [51-21-8], cyclophosphamide [50-18-0], cisplatin [15663-27-1], and mitomycin C (MMC) [50-07-7]. Chemotherapeutic responses to these drugs in each tumor line were as follows: COK-1 (PT) responded to only MMC, while COK-1 (RE) responded to both MMC and cisplatin. However, COK-1 (LN) did not respond to any drug studied. In case of COK-7 (PT) it did not respond to drug as well, though COK-7 (LiM) showed a response to MMC. These results indicate that each tumor line of COK-1 and COK-7 has chemosensitive differences in primary, metastatic, and recurrent tumor lines.

Answer 123:

Bibliographic Information

Experimental and clinical studies on sensitivity test of anticancer agents by 3H-thymidine autoradiography using human malignant tumor transplanted in nude mice. Nishimawari, Kazuharu. Res. Inst. Nuclear Med. Biol., Hiroshima Univ., Hiroshima, Japan. Nippon Geka Gakkai Zasshi (1986), 87(2), 141-53. CODEN: NGGZAK ISSN: 0301-4894. Journal written in Japanese. CAN 105:107845 AN 1986:507845 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The 3H-labeled thymidine [50-89-5] uptake of human xenografts transplanted in nude mice and treated with various anticancer agents was studied by autoradiog. and compared with the histol. changes on the same specimen. Human malignant tumors were transplanted into nude mice and treated with i.p. administration of Mitomycin C (MMC) [50-07-7] 5-Fluorouracil (5-FU) [51-21-8] and Cyclophosphamide (CPM) [50-18-0]. The rate of pos. sensitivity was 65.5% in MMC, 34.9% in 5-FU and 51.8% in CPM by autoradiog. evaluation, while by histol. evaluation 18.9, 14.6, and 16.9%, resp. Apparently, the autoradiog. evaluation of the tumor sensitivity to anticancer agents is more sensitive than the histol. evaluation. As to MMC and CPM, significant correlations were demonstrated between the results of this method and those of the exptl. chemotherapy in accordance with the Battelle Columbus Labs. Protocol using human malignant tumors serially transplanted into nude mice.

Answer 124:

Bibliographic Information

Relationship between 5-fluoro-2'-deoxyuridylate, 2'-deoxyuridylate, and thymidylate synthase activity subsequent to 5-fluorouracil administration, in xenografts of human colon adenocarcinomas. Houghton, Janet A.; Weiss, Karen D.; Williams, Larry G.; Torrance, Pamela M.; Houghton, Peter J. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Biochemical Pharmacology (1986), 35(8), 1351-8. CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 105:90865 AN 1986:490865 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (FUra) [51-21-8] was administered to mice bearing xenografts of human colon adenocarcinomas. In 2 tumor lines,

HxGC3 and HxVRC5, intrinsically resistant to FUra, 2'-deoxyuridylate (dUMP) [964-26-1] accumulated 13.4- and 23.9-fold above basal levels. In HxELC2 xenografts, which demonstrated some sensitivity to FUra, there was a decrease in dUMP concn. after drug administration. Maximal intratumor levels of 5-fluoro-2'-deoxyuridylate (FdUMP) [134-46-3] were found at 1 h, but decreased in all tumor lines by 4 h after administration of FUra. Data derived from tumor cytosols suggested that FdUMP levels in situ were not rate-limiting for formation of covalent ternary complex, but that accumulation of dUMP would retard the rate of complex formation. Subsequent to administration of FUra, thymidylate synthase [9031-61-2] activity was reduced >75% in all tumors, but it recovered rapidly in tumors resistant to FUra. In addn., the pretreatment level of activity of thymidylate synthase was 12.7-fold greater in HxVRC5 tumors than in HxELC2 tumors. This elevated activity in HxVRC5 tumors appears not to be a consequence of gene amplification. Formation of FdUMP or the accumulation of dUMP did not correlate with the activity of phosphatase [9013-05-2] measured at pH 5.8 or pH 9.2 in each tumor line. Further, inhibition of phosphatase activity did not alter the net rate of dissocn. of the FdUMP-thymidylate synthase-[6R]-CH2-H4PteGlu complex.

Answer 125:

Bibliographic Information

Xenografts in pharmacologically immunosuppressed mice as a model to test the chemotherapeutic sensitivity of human tumors. Floersheim, G. L.; Bieri, A.; Chiodetti, Nicole. Zent. Lehre Forsch., Kantonssp., Basel, Switz. International Journal of Cancer (1986), 37(1), 109-14. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 104:81665 AN 1986:81665 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A human tumor xenograft model using pharmacol. immunosuppressed mice was assessed for its suitability to test preclinically the sensitivity of colorectal carcinomas, bone sarcomas and melanomas against anticancer agents. Beside ionizing radiation, 14 cytotoxic drugs including 5-fluorouracil (5-FU) [51-21-8], dimethylmyleran (DMM) [55-93-6], cytosine arabinoside [147-94-4], cyclophosphamide [50-18-0], melphalan [148-82-3], mitomycin C [50-07-7], adriamycin [23214-92-8], bleomycin [11056-06-7], etoposide [33419-42-0], vinblastine [865-21-4], cisplatin [15663-27-1], procarbazine [671-16-9], DTIC [4342-03-4], and BCNU [154-93-8] were assayed. Ionizing radiation, 5-FU and DMM were also applied at LDs followed by bone-marrow rescue high-dose therapy. Four colon carcinomas responded poorly to most of the agents but one tumor displayed marked sensitivity to BCNU. LDs of radiation, 5-FU and DMM and cyclophosphamide and by an osteosarcoma to the latter drug. No strong effects were seen against melanomas. LDs of DMM induced the best regression of one colon carcinoma. In general, the superiority of high-dose therapy for solid human tumors compared to maximally tolerated doses was demonstrated. Individual carcinomas of the same type displayed different drug sensitivity.

Answer 126:

Bibliographic Information

Sequential methotrexate (MTX) and 5-fluorouracil (FU) in human tumor xenografts. Wayss, K.; Herrmann, R.; Mattern, J.; Volm, M. Inst. Exp. Pathol., Ger. Cancer Res. Cent., Heidelberg, Fed. Rep. Ger. Medical Oncology and Tumor Pharmacotherapy (1985), 2(1), 27-32. CODEN: MOTPE2 ISSN: 0736-0118. Journal written in English. CAN 102:214740 AN 1985:214740 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human and animal tumor lines heterotransplanted in nude mice were treated with methotrexate (MTX) [59-05-2] and 5-fluorouracil (FU) [51-21-8] sequentially. In order to investigate the relationship between tumor response and drug toxicity sequence, time and dose of both MTX and FU were varied. Pretreatment with MTX followed by FU at intervals of 3 or 24 h produced superior therapeutic results as compared with single administration of MTX or FU, simultaneous treatment, or the reverse sequence. In the MTX followed by FU regimen, dose redn. of either MTX or FU tended to decrease the antitumor effect. To investigate the toxic effects of different regimens, tumor-free nude mice were treated with MTX and FU the same way as the tumor-bearing animals. In this case, toxicity (wt. loss, leukopenia) was more pronounced in those schedules with the best therapeutic results. However, toxicity appears to be more clearly related to the applied FU dose

Answer 127:

Bibliographic Information

Differential characteristics of two newly established human breast carcinoma cell lines. Chu, Ming Y.; Hagerty, Matthew G.; Wiemann, Michael C.; Tibbetts, Lance M.; Sato, Seiji; Cummings, Frank J.; Bogaars, Hendrik A.; Leduc, Elizabeth H.; Calabresi, Paul. Dep. Med., Roger Williams Gen. Hosp., Providence, RI, USA. Cancer Research (1985), 45(3), 1357-66. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 102:129730 AN 1985:129730 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Two human breast carcinoma cell lines, EP and MW, were established in culture from malignant pleural effusions. In addn. to producing tumors in antithymocyte serum-immunosuppressed mice, both cell lines showed epithelial characteristics and anchorage-independent growth in soft agar. EP and MW differed in morphol. (spindle-shaped vs. round), chromosomal mode (hyperdiploid vs. near triploid), estrogen receptor content (43.8 vs. 5.1 fmol/mg protein), cloning efficiency (0.24 vs. 15%), and activities (milliunits/106 cells) of creatine phosphokinase (25.7 vs. 62.6) and lactate dehydrogenase (346.7 vs. 778.5). Electron microscopy revealed that MW cells had more perinuclear filamentous material and more frequent intracytoplasmic vacuole formation than did EP cells. While having no effect on MW cells at the concns. studied (10-5 to 10-11 M), β-estradiol (10-7 M) stimulated the growth of EP cells by 106% over the hormone-depleted control. In a variety of systems, EP was consistently the more drug-sensitive of the 2 lines. In vitro, EP was significantly more sensitive to methotrexate, vincristine, and 5-fluorouracil, resp. In antithymocyte serum-mouse xenografts, EP displayed a greater response to 3 different dosages of a combination of cyclophosphamide, methotrexate, and 5-fluorouracil. One such dosage (cyclophosphamide, 32.0 mg/kg/day; methotrexate, 13.0 mg/kg/day; 5-fluorouracil, 190.0 mg/kg/day; for 1 day) reduced EP and MW tumor wts. to 5.9 and 41% of controls, resp. These results correlated well with the clin. responses.

Answer 128:

Bibliographic Information

Anticancer drug sensitivity tests using nude mice. Noso, Yoshihiro; Yoshinaka, Ken; Nishimawari, Kazaharu; Hirono, Masashi; Tani, Tadanori; Niimoto, Minoru; Hattori, Takao. Hiroshima Univ., Hiroshima, Japan. Gan no Rinsho (1984), 30(9), 1181-5. CODEN: GANRAE ISSN: 0021-4949. Journal written in Japanese. CAN 102:17009 AN 1985:17009 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Both isotope assay and histol. methods were found useful for the screening of neoplasm inhibitors in nude mice bearing human tumors. The results of the sensitivity study were well correlated with the clin. findings with the testing drugs. The survival rate of patients who received the drugs was higher than that of controls. The drugs used for testing were mitomycin C [50-07-7], 5-fluorouracil [51-21-8], and cyclophosphamide [50-18-0].

Answer 129:

Bibliographic Information

Screening test of antitumor agents by human tumor cell lines in nude mice in ascitic form. Kitahara, Takeshi; Minato, Keisuke; Shimoyama, Masanori. Natl. Cancer Cent. Hosp., Japan. Gan no Rinsho (1984), 30(9), 1158-67. CODEN: GANRAE ISSN: 0021-4949. Journal written in Japanese. CAN 102:17008 AN 1985:17008 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Human breast cancer and leukemic cells implanted in nude mice appeared to be useful models for the screening of neoplasm inhibitors. The sensitivities of implanted tissues to drugs were similar to those found in patients. Studies on the suitable route of administration in these mice provide the best administration routes for humans.

Answer 130:

Bibliographic Information

Effects of 5'-deoxy-5-fluorouridine on human gastrointestinal and breast cancers xenografted to nude mice. Fujita, Fumiko; Fujita, Masahide; Taguchi, Tetsuo. Res. Inst. Microb. Dis., Osaka Univ., Osaka, Japan. Gan to Kagaku Ryoho (1984), 11(8), 1635-43. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 101:183573 AN 1984:583573 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

As a preclin. secondary screening trial, the efficacy of a new deriv. of 5-fluorouracil, 5'-deoxy-5-fluorouridine (5'-DFUR), [3094-09-5] on 15 human cancers xenografted serially to nude mice of BALB/c background was evaluated in comparison with 2 other derivs., tegafur and UFT. Oral administration of 123 mg/kg/day of 5'-DFUR, 25-30 times, produced effective inhibition in 5 out or 7 gastric cancers, 2 out of 3 colorectal cancers, all 3 of breast cancers and 1 out of 2 pancreatic cancers, totalling 11 out of 15 cancer lines (73%) examd. In some cases shrinkage of tumors was noted without any noticeable side effects. Although an increased dose of 185 mg/kg/day of 5'-DFUR resulted in more prominent inhibition on all 9 tumors tested, some animals suffered from severe loss of body wt. or diarrhea. Comparative expts. with equimolar doses of 5'-DFUR(123 mg/kg) and FT-207(100 mg/kg) showed that the inhibition rate of the former was higher than that of the latter in all 8 lines of cancers examd. Six expts. in particular (2 gastric, 1 colorectal, 2 breast and 1 pancreatic cancers), showed that 5'-DFUR statistically sustained more effective suppression. Direct comparisons of 5'-DFUR and UFT were also made in 5 expts. in which 3 cancers were more sensitive to the former drug. Promising results in clin. trials can be expected with the new drug 5'-DFUR for these kinds of cancers.

Answer 131:

Bibliographic Information

Increased cytotoxic effects of various anticancer drugs by α-interferon (HLBI) on human tumor xenografts in nude mice. Nosoh, Yoshihiro; Yoshinaka, Ken; Yamaguchi, Masahiro; Tani, Tadanori; Toge, Tetsuya; Niimoto, Minoru; Hattori, Takao. Res. Inst. Nucl. Med. Biol., Hiroshima Univ., Hiroshima, Japan. Gan to Kagaku Ryoho (1984), 11(8), 1623-8. CODEN: GTKRDX ISSN: 0385-0684. Journal written in Japanese. CAN 101:163319 AN 1984:563319 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of 7 anticancer agents in combination with interferon on gastric cancer and malignant melanoma of human transplanted s.c. in nude mice was studied. Of the 7 drugs, mitomycin C [50-07-7] and adriamycin [23214-92-8] showed the greatest inhibition of tumor growth in combination with interferon.

Answer 132:

Bibliographic Information

Comparative data from experimental chemotherapy of human tumor xenografts in nude mice, and the clinical responses of the patient-donors. Taguchi, Tetsuo; Fujita, Masahide. Univ. Osaka, Osaka, Japan. Eksperimental'naya i Klinicheskaya

Farmakoterapiya (1983), 12 77-83. CODEN: EKFMA7 ISSN: 0367-0589. Journal written in Russian. CAN 100:167828 AN 1984:167828 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A high degree of correlation was found between the effects of ftorafur [17902-23-7] in combination with MFC (mitomycin C [50-07-7], 5-fluorouracil [51-21-8], and cytosine arabinoside [147-94-4]) on the growth of tumor xenografts of 3 different human tumors in nude mice and the effects of the same chemotherapy on the patient-donors of the cell lines.

Answer 133:

Bibliographic Information

Renal cell carcinoma - xenotransplantation into immuno-suppressed mice. Kopper, L.; Magyarosy, E.; Nagy, P.; Lapis, K.; Szamel, I.; Eckhardt, S.; Csata, S.; Wabrosch, G.; Repassy, D. 1st Inst. Pathol. Exp. Cancer Res., Semmelweis Med. Univ., Budapest, Hung. Oncology (1984), 41(1), 19-24. CODEN: ONCOBS ISSN: 0030-2414. Journal written in English. CAN 100:150726 AN 1984:150726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Twenty one human renal cell carcinomas (RCC) were xenotransplanted into artificially immunosuppressed mice. Four tumors grew successfully retaining some characteristics of the primary tumors (according to morphol. and karyotype anal.), but losing metastatic capacity. One of the serially transplantable tumors (HT 40) with hyperdiploid cellular DNA content and estrogen receptor positivity failed to respond to the single maximally tolerated dose of several cytotoxic agents.

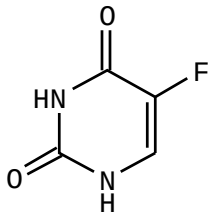
Answer 134:

Bibliographic Information

Elucidation of pathways of 5-fluorouracil metabolism in xenografts of human colorectal adenocarcinoma. Houghton, Janet A.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. European Journal of Cancer & Clinical Oncology (1983), 19(6), 807-15. CODEN: EJCODS ISSN: 0277-5379. Journal written in English. CAN 99:82015 AN 1983:482015 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of hypoxanthine (Hx) [68-94-0] and allopurinol (HPP) [315-30-0] on the metab. of 6-3H-labeled 5-fluorouracil (FUra) (I) [51-21-8] was examd. in 5 human colorectal adenocarcinomas maintained as xenografts in immune-deprived mice. In 2 tumors the formation of ribonucleotides from FUra was depressed by Hx and HPP in combination during the 1st h after treatment, while in the 3 other lines ribonucleotide concns. were not reduced. The 5 xenograft lines may be divided into 2 groups. Group-1 tumors formed relatively. high levels of 5-fluorouridine (FUrd) [316-46-1] and low levels of fluorinated ribonucleotides after the injection of FUra, with no decrease in ribonucleotide concns. after the administration of Hx and HPP. These tumors possessed high ratios of uridine phosphorylase [9030-22-2]/orotate phosphoribosyltransferase (OPRTase) [9030-25-5], and ribose 1-phosphate (R-1-P) [14075-00-4]/5-phosphoribosyl 1-pyrophosphate (PRPP) [7540-64-9] and thus appeared to metabolize FUra by the uridine phosphorylase and kinase pathway. Group-2 tumors formed low levels of FUrd, higher concns. of fluorinated ribonucleotides, and a redn. in levels of these nucleotides after administration of the purine combination. Group-2 tumors demonstrated a lower enzyme ratio, higher endogenous levels of PRPP, and a lower R-1-P/PRPP ratio, and appeared to metabolize FUra predominantly by the activity of OPRTase. Hx and HPP, alone or in combination, caused a rapid depletion of PRPP in each tumor line examd. In group-2 tumors this may be responsible for the decreased formation of FUra ribonucleotides obsd.



I

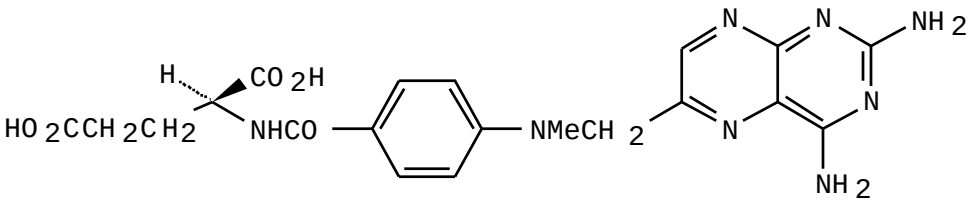
Answer 135:

Bibliographic Information

The selectivity of action of methotrexate in combination with 5-fluorouracil in xenografts of human colon adenocarcinomas. Houghton, Janet A.; Tice, Arvil J.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Molecular Pharmacology (1982), 22(3), 771-8. CODEN: MOPMA3 ISSN: 0026-895X. Journal written in English. CAN 98:209664 AN 1983:209664 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The possibility for increasing the therapeutic index in the treatment of human colon adenocarcinomas maintained as xenografts in immune deprived mice using combinations of methotrexate (I) [59-05-2] that preceded 5-fluorouracil (II) [51-21-8] was studied. I, at a dose of 100 mg/kg, increased the 5-phosphoribosyl-1-pyrophosphate (PRPP) [7540-64-9] concn. in 3 colon xenograft lines to a max. between 14 and 24 h after treatment. In murine bone marrow, concns. of PRPP decreased progressively after I treatment, but in ileum there was a dramatic increase such that by 4 h PRPP was 968% of control. The metab. of II-63H administrated 24 h after I was increased in ileum and resulted in an increased rate and a greater level of incorporation of II-63H into RNA. Only a slight elevation in the incorporation of II-63H into the RNA of one tumor line (HxELC,2) was obsd. The scheduling of II at a dose level of 25 mg/kg 24 h after a priming dose of I (100 mg/kg) was at least as toxic as 100 mg of II/kg administered alone. The dose-limiting toxicity was related to gastrointestinal damage; no bone marrow toxicity was detected. At ≤100 mgI/kg, the increase in PRPP obtained in gastrointestinal tissue was greater than that obsd. in human colon xenografts 24 h after treatment. A basis for increasing the therapeutic efficacy of II through a selective increase in tumor PRPP using I was not obtained in these studies.



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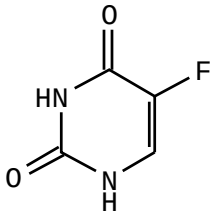


II

Answer 136:

Bibliographic Information

New method for evaluating the effect of experimental chemotherapy on human xenografts in nude mice: use of lactate dehydrogenase isozyme. Hayata, Satoshi; Fujita, Masahide; Nakano, Yosuke; Kumagai, Michihiko; Hakozaki, Michinori; Taguchi, Tetsuo. Res. Inst. Microbial Dis., Osaka Univ., Osaka, Japan. Editor(s): Periti, Piero; Gialdroni Grassi, Giuliana. Curr. Chemother. Immunother., Proc. Int. Congr. Chemother., 12th (1982), Meeting Date 1981, 2 1283-4. Publisher: Am. Soc. Microbiol., Washington, D. C CODEN: 48HGAR Conference written in English. CAN 97:174303 AN 1982:574303 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Monitoring human lactate dehydrogenase (I) [9001-60-9] isozyme 5 during chemotherapy in the nude mouse was more sensitive than conventional methods for evaluation of treatment. In H-55 (gastric) and H-62 (breast) tumors, good correlation between tumor vols. and human I were obsd. and the coeffs. were 0.686 and 0.803, resp. H-81 gastric cancer was very sensitive to TA-077 [70189-62-7] (100 mg/kg, weekly). S.c. tumor decreased after treatment and almost disappeared at the termination of the expt. Human I also decreased, and this decrease was greater than that obsd. for tumor size. The I isozyme method was more sensitive than the measurement of tumor size. In the ascitic tumor (Br-13 breast cancer) system, the effect of drugs was easily detd. by the human I level.

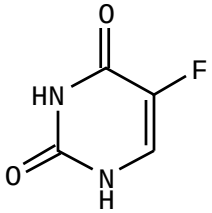
Answer 137:

Bibliographic Information

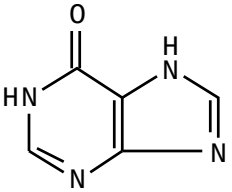
Combinations of 5-FU, hypoxanthine, and allopurinol in chemotherapy for human colon adenocarcinoma xenografts. Houghton, Janet A.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp., Memphis, TN, USA. Cancer Treatment Reports (1982), 66(5), 1201-6. CODEN: CTRRDO ISSN: 0361-5960. Journal written in English. CAN 96:210551 AN 1982:210551 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A series of 4 human colon adenocarcinomas, growing as xenografts in immune-deprived mice, have been used to evaluate the efficiency of 5-FU (I) [51-21-8] in combination with hypoxanthine (Hxt)(II) [68-94-0] and allopurinol (HPP)(III) [315-30-0], used to reduce the toxicity of 5-FU in host mice. Tumor-bearing mice were treated at 7-day intervals with 5-FU administered simultaneously with the protecting agents (Hx and HPP). Two tumor lines (HxVRC5 and HxGC3), insensitive to 5-FU alone, failed to show any response to this combination. In 5-FU-sensitive HxELC2 tumors, the combination of 5-FU with Hx and HPP did not increase the therapeutic index, and in HxHC1 xenografts, antagonism to 5-FU cytotoxicity was obsd. Tumor response in relation to the pathways of 5-FU metab. is discussed.



I



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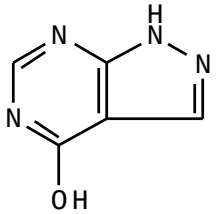


III

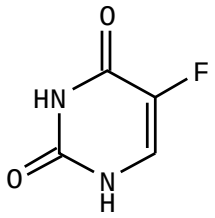
Answer 138:

Bibliographic Information

Studies in an animal model on the effectiveness of adjuvant chemotherapy with 5-FU and BCNU in cases of colorectal adenocarcinoma. Schmitz, R.; Hueiper, J.; Pichlmayr, R. Klin. Abdom. Transplantationschir., Med. Hochsch. Hannover, Hannover, Fed. Rep. Ger. Journal of Cancer Research and Clinical Oncology (1981), 100(2), 213-20. CODEN: JCROD7 ISSN: 0171-5216. Journal written in English. CAN 95:73492 AN 1981:473492 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effect of combined chemotherapy with 5-FU (5-fluorouracil) (I) [51-21-8] and BCNU [154-93-8] on well-differentiated human adenocarcinomas of different stages following xenotransplantation and growth in syngeneic balb/c nude mice collectives was investigated. With a tumor take of approx. 90%, marked remissions of ≤43% of the original vol. were obtained only with those transplant tumors initially classified as Dukes A and B; carcinomas graded Dukes C/D underwent no significant remission. Pathohistol. findings during tumor remission revealed large amts. of fibrotic tissue, together with surviving nests of tumor cells.



I

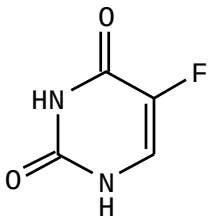
Answer 139:

Bibliographic Information

Chemotherapy of human colorectal tumor xenografts in athymic mice with clinically active drugs: 5-fluorouracil and 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU). Comparison with doxorubicin derivatives: 4'-deoxydoxorubicin and 4'-O-methyldoxorubicin. Giuliani, Fernando C.; Zirvi, Karimullah A.; Kaplan, Nathan O.; Goldin, Abraham. Cancer Cent., Univ. California, La Jolla, CA, USA. International Journal of Cancer (1981), 27(1), 5-13. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 94:185489 AN 1981:185489 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects of single-agent therapy with 2 clin. useful drugs 5-fluorouracil (5-FU)(I) [51-21-8] and BCNU [154-93-8], against human colorectal tumors (rectum T 157 and T 348, lung metastasis T 84, lymph-node metastasis T 245, colon, T 183, T 219, T 347, T 362 and T 380) transplanted and passed serially in athymic (nude) mice were studied. In addn., chemosensitivity of the tumors to 5-FU and BCNU was compared with the chemosensitivity of the tumors to 2 new doxorubicin analogs, 4'-deoxydoxorubicin (II) [63521-85-7] and 4'-O-methyldoxorubicin (III) [77121-90-5]. BALB/c nude mice were treated i.v. on a weekly basis for 3-4 wk, starting when the tumor vol. became relatively large (advanced stage of tumor treatment). All the tumors showed a 90-100% take rate and stable growth. In these expts., 77% of the colorectal tumors were biol. sensitive to the treatment with 5-FU, but the percentage of statistically significant sensitive tumors was 22%, which is in good agreement with the clin. data reported in the literature (21%). In patients, BCNU has been reported to give up 13% response. In contrast, a 33% statistically significant response rate was found in our panel of colorectal tumors. The difference could be related to the higher tolerance of nude mice to certain drugs, including BCNU. Apparently, the 2 new doxorubicin derivs., 4'-deoxydoxorubicin and 4'-O-methyl-doxorubicin, should be more active in the patient than both of the clin. used drugs, 5-FU and BCNU. Furthermore, there is a good correlation between the results obtained in the exptl. system (human tumor/nude mouse) and in human patients with the active drugs, 5-FU and BCNU.



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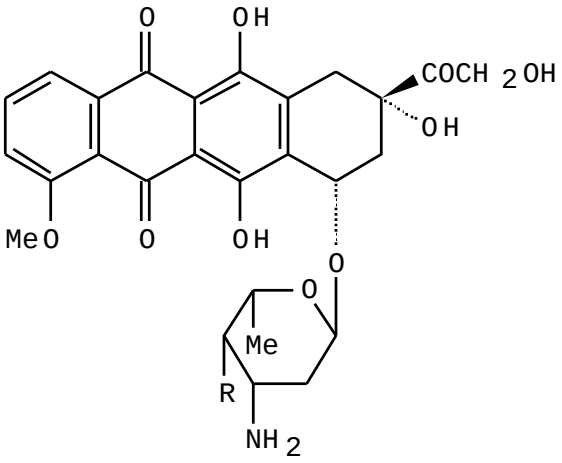


II, R=H

III, R=OMe

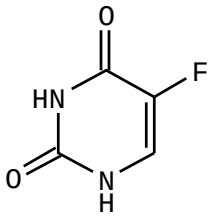
Answer 140:

Bibliographic Information

Biochemical determinants of responsiveness to 5-fluorouracil and its derivatives in xenografts of human colorectal adenocarcinomas in mice. Houghton, Janet A.; Maroda, Stephen J., Jr.; Phillips, John O.; Houghton, Peter J. Div. Biochem. Clin. Pharmacol., St. Jude Children's Res. Hosp., Memphis, TN, USA. Cancer Research (1981), 41(1), 144-9. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 94:95907 AN 1981:95907 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The level of thymidylate synthetase (EC 2.1.1.45) [9031-61-2] and its activity were measured in a series of human colorectal adenocarcinomas growing as xenografts in immune-deprived mice. Enzyme activity varied between 8.4 and 124 pmol/mg protein/h; within each tumor line, this activity correlated with the capacity to bind 3H-labeled 5-fluoro-2'-deoxyuridine 5'-monophosphate ([6-3H]FdUMP) [134-46-3], which varied between 0.16 and 1.68 pmol [6-3H]FdUMP bound per g tissue. Highest and lowest activities were measured in tumor lines that were insensitive to 5-fluorouracil (I) [51-21-8], 5-fluorouridine [316-46-1], and 5-fluoro-2'-deoxyuridine [50-91-9]. The ratio of the max. free FdUMP concn. to thymidine 5'-monophosphate synthetase-binding activity did not differentiate fluorinated pyrimidine-responsive lines from those innately insensitive. Max. potential binding of [6-3H]FdUMP in vitro was measured without addn. of dl-L-5,10-methylenetetrahydrofolate (CH2FH4) in cytosol from 2 tumor lines, both of which demonstrated some sensitivity to fluorinated pyrimidine therapy. The other 4 insensitive tumor lines required CH2FH4 to be added in order to attain max. [6-3H]FdUMP binding. Similar data were obtained using nitrocellulose membrane filtration to isolate both covalent and noncovalent complexes. Direct measurement of thymidine 5'-monophosphate synthetase activity after incubation of tumor cytosols with FdUMP, with or without added CH2FH4, showed that, in nonresponsive tumors, max. enzyme inhibition was achieved only in the presence of exogenous cofactor. It is suggested that the availability of cofactor may prove important in the formation of the ternary complex CH2FH4-thymidine 5'-monophosphate synthetase-FdUMP when high concns. of FdUMP are present for only short periods of time.



I

Answer 141:

Bibliographic Information

Chemotherapy of human breast-carcinoma xenografts. Bailey, M. J.; Gazet, J. C.; Smith, I. E.; Steel, G. G. Inst. Cancer Res., Sutton/Surrey, UK. British Journal of Cancer (1980), 42(4), 530-6. CODEN: BJCAAI ISSN: 0007-0920. Journal written in English. CAN 94:95754 AN 1981:95754 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Sensitivities were varied for 5 lines of human breast carcinoma xenografts, grown and passaged in immune-suppressed mice, to cyclophosphamide [50-18-0], methotrexate [59-05-2], 5-fluorouracil [51-21-8], adriamycin [23214-92-8], vincristine [57-22-7], and melphalan [148-82-3], alone and in combination. The most effective single agent or combination differed for each tumor. This system may be useful for testing new cytotoxic agents and predicting clin. chemotherapy response.

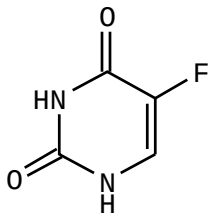
Answer 142:

Bibliographic Information

5-Fluorouracil in combination with hypoxanthine and allopurinol: toxicity and metabolism in xenografts of human colonic carcinomas in mice. Houghton, Janet A.; Houghton, Peter J. Dep. Biochem. Clin. Pharmacol., St. Jude Child. Res. Hosp,., Memphis, TN, USA. Biochemical Pharmacology (1980), 29(14), 2077-80. CODEN: BCPCA6 ISSN: 0006-2952. Journal written in English. CAN 94:24654 AN 1981:24654 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

I.p. administration of 5-FU (I) [51-21-8] (400 mg/kg) with hypoxanthine (II) [68-94-0] (50 mg/kg) or allopurinol (III) [315-30-0] or both to mice reduced gastrointestinal and bone-marrow toxicities over 20 days as compared with I treatment alone. After I-6-3H administration (100 mg/kg) to mice with I-sensitive tumors, the concn. of intratumor I metabolites was raised by concomitant administration of II and III; in I-insensitive-tumor-bearing mice, III caused a slight elevation in I metabolite levels, II caused a significant rise, and II and III together a larger rise. In the latter, an increase in 5-fluoro-dUMP [134-46-3], 5-fluoro-UMP [796-66-7], and 5-fluorouridine [316-46-1] was obsd. after II and III administration, but 5-fluoro-UTP [73231-43-3] and 5-fluoro-UDP [803-98-5] levels decreased.



I

Answer 143:

Bibliographic Information

Use of heterotransplants in diffusion chambers for determining the individual drug sensitivity of human ovarian cancer to chemotherapeutic drugs. Sobol, I. L.; Marenich, A. F. Cancer Res. Cent., Moscow, USSR. Byulleten Eksperimental'noi Biologii i Meditsiny (1979), 88(8), 243-5. CODEN: BEBMAE ISSN: 0365-9615. Journal written in Russian. CAN 91:150972 AN 1979:550972 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The sensitivity of 10 ovarian tumor heterotransplants in diffusion chambers in mice to hexamethylmelamine [645-05-6], cyclophosphane [50-18-0], 5-fluorouracil [51-21-8], methotrexate [59-05-2], dactinomycin [50-76-0], 17-hydroxyprogesterone caproate [630-56-8], and thiotepa [52-24-4] was variable. E.g., hexamethylmelamine, cyclophosphane, 5-fluorouracil, and methotrexate had a brief inhibiting effect in growth of a solid glandular cancer, inhibited growth of a glandular papillary cancer, and had no effect on growth of a papillary adenocarcinoma. In 4 of 5 cases where results of these expts. were compared with results of expts. obtained in the treatment of patients with the same drugs, exptl. results correlated with clin. findings.

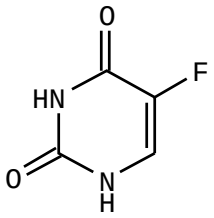
Answer 144:

Bibliographic Information

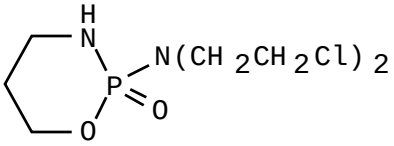
Chemotherapy of Nb rat adenocarcinoma of the prostate heterotransplanted into congenitally athymic (nude) mice: report of 5-fluorouracil and cyclophosphamide. Drago, Joseph R.; Maurer, Robert E.; Gershwin, M. Eric; Eckels, David D.; Goldman, Laurence B. Dep. Urol., Univ. California, Davis, CA, USA. Journal of Surgical Research (1979), 26(4), 400-3. CODEN: JSGRA2 ISSN: 0022-4804. Journal written in English. CAN 91:83171 AN 1979:483171 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (I) [51-21-8] (80 mg/kg) injected i.p. once into congenitally athymic (nude) mice bearing rat prostatic adenocarcinoma produced marked tumor regression. Cyclophosphamide (II) [50-18-0] (100 mg/kg/day) injected i.p. for 7 days into athymic mice with an autonomous tumor inhibited tumor growth but was not as effective as I.



I



II

Answer 145:

Bibliographic Information

Study of the anti-tumor effect of anti-vascular endothelial growth factor McAb 5-fluorouracil loaded polylactic acid nanoparticles. Huang Kai-hong; Liu Jian-hua; Wang Lin-yun; Zhu Zhao-hua; Chen Qi-kui; Min Jun; Chen Ru-fu Institute of Gastroenterology, The Second Affiliated Hospital, Sun Yat-sen University, Guangzhou 510120, China Zhonghua wei chang wai ke za zhi = Chinese journal of gastrointestinal surgery (2007), 10(5), 482-5. Journal code: 101177990. ISSN:1671-0274. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Chinese. PubMed ID 17851795 AN 2007536910 In-process for MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVE: To explore the anti-tumor efficacy of anti- vascular endothelial growth factor (VEGF) McAb 5-fluorouracil (5-FU) loaded polylactic acid (PLA) nanoparticles (NPS) in human gastric carcinoma xenografts of nude mice. METHODS: Anti-VEGF McAb 5-FU loaded PLA NPS were made by ultrasound emulsification. Nude mice model of human gastric carcinoma xenografts was established. Therapeutic effects of drugs on human gastric carcinoma xenografts and side effects concerned were observed. RESULTS: The tumor inhibition rates of control group, nanosphere without 5-FU group, 5-FU (20 mg/kg) group, anti-VEGF McAb nanosphere without 5-FU group, anti-VEGF McAb group, nanosphere with 5-FU group, 5-FU (20 mg/kg) combined with anti-VEGF McAb group, anti-VEGF McAb 5-FU loaded nanosphere group was

0, 6.61%, 24.26%, 27.94%, 35.29%, 37.50%, 39.71% and 52.21% respectively, and there were no significant differences between anti-VEGF McAb 5-FU loaded nanosphere group and nanosphere group without 5-FU in WBC count, serum alanine transferase level or creatinine level. Compared with control group and anti-VEGF McAb 5-FU loaded nanosphere group, the 5-FU group decreased by 34.43% and 37.38% respectively in WBC count (P< 0.05), and increased by 93.17% and 66.56% respectively in alanine transferase. There were significant differences between experimental groups and control group in apoptosis index, especially between anti-VEGF McAb 5-FU loaded nanosphere group and control group (P< 0.05). The microvessel density (MVD) of experimental groups containing anti-VEGF McAb was significantly lower than that of control group or groups containing 5-FU (P< 0.05). CONCLUSION: Anti-VEGF McAb 5-FU loaded nanosphere can increase the tumor inhibitory rate of 5-FU, induce apoptosis by inhibiting tumor angiogenesis with less side effect, and then enhance therapeutic effect, which indicate its potential as a novel, safe nano-tumor-targeting drug.

Answer 146:

Bibliographic Information

Higher dose and dose-rate in smaller tumors result in improved tumor control. Mayer A; Tsiompanou E; Flynn A A; Pedley R B; Dearling J; Boden R; Begent R H J Cancer Research UK Targeting and Imaging Group, Department of Oncology, Royal Free Campus, Royal Free and University College Medical School, University College London, London, UK. a.mayer@ucl.ac.uk Cancer investigation (2003), 21(3), 382-8. Journal code: 8307154. ISSN:0735-7907. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 12901284 AN 2003367736 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Small tumors are more sensitive to radioimmunotherapy (RIT) than larger ones. A greater proportion of viable radiosensitive areas in small tumors, higher antibody uptake, and radiation dose may be responsible. Six groups of mice with small (median tumor size 0.06 cm3) or large LoVo xenografts (median tumor size 0.38 cm3) received either RIT using a 131I-labeled anti-CEA antibody A5B7, 5-fluorouracil (5-FU) modulated with folinic acid (FA), or no treatment. The % injected activity/gram, antibody distribution in viable and necrotic areas, and dose distribution were determined. High-power microscopy images of the original section were reconstructed to estimate the proportion of viable areas. Mice with small and large tumors grew significantly less rapidly when treated with RIT compared to the control group ($p < 0.0004$ and $p < 0.003$, respectively), while 5-FU was ineffective. Small tumors treated with RIT grew less than large tumors ($p < 0.02$). A higher amount of % injected activity/gram of tumor (median 26.6% vs. 8.1%, $p = 0.0007$) and a higher dose-rate were found in small tumors at 24 hours post injection (viable areas: 56.2 +/- 23.7 vs. 13.3 +/- 7 cGy/h, necrosis 19.2 +/- 16.3 vs. 4.9 +/- 4.7 cGy/h, $p = 0.0007$). It appears that as viable tumor masses grow the access to them decreases and this has a fourfold effect on dose delivered for RIT in this example. These data support the consideration of use of RIT for adjuvant treatment in colon cancer.

Answer 147:

Bibliographic Information

Influence of combination of low dosage 131I-labeled anti-carcinoembryonic antigen antibody C50 and 5-fluorouracil on tumor growth of colorectal cancer xenografts in nude mice. Zheng Chao-Xu; Zhan Wen-Hua; Cai Shi-Rong; He Yu-Long; Lin Zhan-Jiang Department of General Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, Guangdong, PRChina. zcxzd@163.net Ai zheng = Aizheng = Chinese journal of cancer (2003), 22(4), 354-7. Journal code: 9424852. ISSN:1000-467X. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in Chinese. PubMed ID 12703987 AN 2003185180 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND & OBJECTIVE: The aim of this study was to investigate the influence of low dosage (131)I-labeled anti-carcinoembryonic antigen (CEA) monoclonal antibody C50 ((131)I-C50) on tumor growth and the therapeutic efficacy of combination of low dosage (131)I-C50 with chemotherapy using 5-fluorouracil (5-FU) on human colorectal cancer xenografts in nude mice. METHODS: Human colorectal cancer xenografts with positive CEA expression were established in nude mice with LoVo cell line. 5-FU, 2,775 kBq (131)I-C50, and 5-FU combined with (131)I-C50 were given to nude mice through tail vein to treat xenografts at 9(th) day after implantation of tumor cells. Two of the mice of each group were sacrificed randomly at 7(th) day after the treatment; and cellular ultrastructure of tumor tissues was examined under electron microscope. Pathological changes of tumor tissues were examined under light microscope. Tumor volume, tumor doubling time, and inhibition rate of each group were calculated. Tumor volumes of all groups at 30(th) day after implantation were compared with each other. RESULTS: There was significant difference of tumor volumes at 30(th) day after implantation between each other among control group, chemotherapy group, radioimmunotherapy (RAIT) group, and RAIT+chemotherapy group (P< 0.001). Tumor doubling time of these groups was prolonged and tumor inhibition rates increased successively. CONCLUSION: Low dosage (131)I-C50 can inhibit tumor growth of human colorectal cancer xenografts in nude mice. Efficacy of tumor growth inhibition can be enhanced by combination of low dosage (131)I-C50 with chemotherapy.

Answer 148:

Bibliographic Information

The antioxidant n-acetylcysteine increases 5-fluorouracil activity against colorectal cancer xenografts in nude mice. Bach S P; Williamson S E; Marshman E; Kumar S; O'Dwyer S T; Potten C S; Watson A J Cancer Research Campaign, Department of Epithelial Biology, The Paterson Institute, Christie Hospital, Withington, Manchester M20 4BX, UK. Sbach@picr.man.ac.uk Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract (2001), 5(1), 91-7. Journal code: 9706084. ISSN:1091-255X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11309653 AN 2001213592 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antioxidant pyrrolidinedithiocarbamate improves the therapeutic efficacy of 5-fluorouracil (5-FU) against HCT-15 colorectal cancer cell line xenografts in nude mice without increasing toxicity to normal intestinal or hematopoietic tissues. In the current study we have shown that a similar clinically licensed antioxidant, N-acetylcysteine (200 mg/kg), can modulate the activity of 5-FU (120 mg/kg) against HCT-15 tumor xenografts in nude mice. We demonstrate that this effect is accompanied by a sustained elevation in p53-independent apoptosis without accompanying alterations in cell cycle kinetics. Extensive tumor necrosis is also a prominent feature of treatment; however, no significant impairment of neovascularization as assessed by intratumor microvessel density occurred. We believe that the clinical efficacy of N-acetylcysteine as an adjunct to 5-FU in advanced colorectal cancer should be investigated further.

Answer 149:

Bibliographic Information

Establishment of a human pancreatic tumor xenograft model: potential application for preclinical evaluation of novel therapeutic agents. Mohammad R M; Dugan M C; Mohamed A N; Almatchy V P; Flake T M; Dergham S T; Shields A F; Al-Katib A A; Vaitkevicius V K; Sarkar F H Department of Internal Medicine, Wayne State University School of Medicine, Karmanos Cancer Institute, Detroit, Michigan 48201, USA Pancreas (1998), 16(1), 19-25. Journal code: 8608542. ISSN:0885-3177. (CASE REPORTS); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9436858 AN 1998097358 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Adenocarcinoma of the pancreas is currently the fifth leading cause of death in the United States. It remains generally incurable by available treatment modalities. We report here on the characterization of a permanent pancreatic cell line (KCI-MOH1), established as a xenograft in severe combined immune deficient (SCID) mice, from a 74 year-old African American male patient diagnosed with pancreatic cancer. Sections from paraffin-embedded tumors excised from SCID mice revealed typical adenocarcinoma of the pancreas. Karyotypic analysis of cultured cells derived from tumors grown in SCID mice revealed a male karyotype with multiple clonal aberrations: 42, XY, add (3)(p11.2), der(7) t(7;12) (p22;q12), -10, -12, add (14)(p11), -18, add (20)(q13)-22/84, idemx2. Immunostaining of KCI-MOH1 tissues shows strong expression of p53 and p21 proteins. The xenograft model was established by transplanting the KCI-MOH1 cells subcutaneously (s.c.) in SCID mice. When the s.c. tumor was transplanted in vivo to other SCID mice, the success rate was 100%, with a doubling time of 8.5 days. The SCID mouse xenograft model was used to test the efficacy of selected standard chemotherapeutic drugs (taxol, gemcitabine, 5-fluorouracil, and Ara-C) and novel biological agents (Bryostatin 1 and Auristatin-PE). Results show that gemcitabine, Ara-C, and Bryostatin 1 were active against KCI-MOH1. The xenograft described herein can be used as an animal model to facilitate the development of novel therapeutic agents against human pancreatic cancers.

Answer 150:

Bibliographic Information

Biochemical modulation applied to experimental cancer chemotherapy. Nakamura Y Department of Otolaryngology, Teikyo University, School of Medicine, Tokyo Nippon Jibiinkoka Gakkai kaiho (1996), 99(11), 1694-704. Journal code: 7505728. ISSN:0030-6622. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8969073 AN 97123842 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The biochemical modulation (BCM) of the antitumor effect of 5-fluorouracil (5-FU) by leucovorin (LV) was studied with xenografts (MC-1, MC-3, MPC-2) by transplanting human tumors to nude mice and by human tumor clonogenic assay (HTCA). For human tumor transplantation to nude mice, the dose of 5-FU was set at LD50 x 0.6 or LD50 x 0.8 and LV was given in three doses, 0.45, 0.15, 0.06 mg/body. Antitumor effects of combined administration of 5-FU and LV at the same time, as compared with that of administration of LV one hour before 5-FU, were examined. The relationship between the rate of inhibition of thymidylate synthetase (T.S) activity and 5-FU concentration in the neoplastic tissues was also examined. In HTCA the antitumor effects of 5-FU were examined by two methods: 1) limited contact for one four, and 2) continuous contact for two weeks. In the human tumor transplantation to nude mice, the BCM of the antitumor effect of 5-FU by LV was demonstrated in MC-1 and MPC-2. This BCM function of LV was enhanced by administering it one hour before 5-FU. The suitable LV dose was between 0.15 and 0.45 mg/body. Although there was a tendency for the rate of inhibition of T.S to be proportional to the tissue concentration of 5-FU, there was no significant relationship between the T.S inhibition rate and the antitumor effect. In HTCA, the BCM function of LV was suggested by the two-week-continuous contact method with MC-1 and MPC-2. Depending on the method of administering LV, the antitumor activity was higher with two-week continuous contact than with one-hour contact. In conclusion, the BCM effect of LV on the antitumor effect of 5-FU was revealed in MC-1 and MPC-2 strains. Further studies are needed to establish a standard for appropriate dosage and administration of LV.

Answer 151:

Bibliographic Information

Inhibition of experimental liver metastasis by combined treatment with tamoxifen and interferon. Werner A; Bender E; Mahaffey W; McKeating J; Marrangoni A; Katoh A Department of Surgery, Mercy Hospital, Pittsburgh, PA 15219, USA Anti-cancer drugs (1996), 7(3), 307-11. Journal code: 9100823. ISSN:0959-4973. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8792005 AN 96384107 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The demonstration of estrogen receptors (ERs) in the liver has established it as a hormonally responsive organ. Estrogens have been imputed to have a role in the development of benign and malignant liver tumors. The detection of ERs in samples of normal liver tissue and in hepatocellular carcinomas suggested a treatment strategy with anti-hormonal drugs, i.e. tamoxifen, as used clinically for the treatment of breast cancer. The objective of this study was to test the effect of tamoxifen and tamoxifen in combination with other agents [5-fluorouracil (5-FU) and interferon (IFN)] against experimental liver metastases of human colorectal tumor cells xenografted into nude mice. A human colorectal tumor cell line, LoVo, was injected into the spleens of nude mice. This produces liver metastases in virtually 100% of the mice in 6-8 weeks. One week before tumor cell implantation, all mice were ovariectomized. Treatment was started 3 days after the intrasplenic injections. This consisted of 5 mg tamoxifen pellets (60-day release) implanted s.c., 5-FU given i.p. once a week for 4 weeks on a 46 mg/kg basis and IFN given s.c., daily for 4 weeks, 3 x 10(5) units/injection. The effect of tamoxifen alone on liver metastases was not significantly different from untreated controls. Tamoxifen in combination with IFN and 5-FU, however, resulted in 50-67% inhibition of liver metastases, as compared with the controls. The effectiveness of the treatment was in the order: tamoxifen + IFN > tamoxifen + 5-FU + IFN > tamoxifen + 5-FU. Thus, IFN may be useful as a potentiating agent in combination with tamoxifen for the treatment of estrogen-dependent tumors.

Answer 152:

Bibliographic Information

Experimental chemoendocrine therapy of human breast carcinoma xenograft serially transplanted into nude mice. Watanabe O Department of Surgery, Tokyo Women's Medical College Daini Hospital Nippon Geka Gakkai zasshi (1994), 95(4), 263-70. Journal code: 0405405. ISSN:0301-4894. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 7910941 AN 94254805 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antitumor effect of combined chemoendocrine therapy with tamoxifen (TAM) and 5-fluorouracil (5-FU) on breast carcinoma xenograft (R-27), serially transplanted into the nude mice, was examined from the aspect of estrogen receptors (ER) and cytological features. The mice were given 6 intramuscular injections of TAM (5mg/kg) at 3-day intervals (TAM group), 3 intraperitoneal injections of 5-FU (60 mg/kg) at 4-day intervals ((5-FU group), or a combination of the two drugs (combined group). When the tumor was resected on 21 days after the initial treatment, the ER were assayed and %S was determined by flowcytometry. Furthermore, proliferative cell nuclear antigen (PCNA) was stained, and the stained cells were counted. A synergistic antitumor effect of TAN and 5-FU was found in mice given combined therapy. Reduction in the ER level was more marked in this group than in the others, but there were no significant differences in the %S value or the ratio of PCNA positive cells among the three treated groups. These results suggest that the combined effect of TAM and 5-FU has no relation to the inhibition of DNA synthesis.

Answer 153:

Bibliographic Information

Modulation by 1-leucovorin of 5-fluorouracil antitumor activity on human gastric carcinoma xenograft in nude mouse: preliminary report. Kase S; Kubota T; Furukawa T; Watanabe M; Teramoto T; Ishibiki K; Kitajima M Department of Surgery, School of Medicine, Keio University, Tokyo, Japan Nippon Geka Gakkai zasshi (1993), 94(6), 659. Journal code: 0405405. ISSN:0301-4894. Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 8341253 AN 93341444 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 154:

Bibliographic Information

Interferon alpha-2a shows antitumor activity in combination with 5-fluorouracil against human colon carcinoma xenografts: a study in reference to thymidylate synthetase activity inhibition. Kubota T; Inada T; Ogata Y Department of Surgery, School of Medicine, Keio University, Tokyo, Japan Surgery today (1992), 22(5), 481-3. Journal code: 9204360. ISSN:0941-1291. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1421872 AN 93043976 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To clarify the mode of antitumor activity shown by a combination of recombinant human interferon alpha-2a (IFN) and 5-fluorouracil (5-FU), experimental therapy was performed on human colon carcinoma (Co-4) xenografts serially transplanted into nude mice, using IFN and 5-FU, either alone or in combination. IFN alone showed dose-dependent antitumor activity and 5-FU also revealed a moderate antitumor effect. Although IFN, given as 600,000 units/mouse daily sc x 14, and 5-FU, given as 60 mg/kg q4d x 3 ip, showed additive antitumor activity against Co-4, the thymidylate synthetase (TS) inhibition rate was unchanged in the tumors treated with the IFN/5-FU combination in comparison with those treated with 5-FU alone. This suggests that the antitumor activity of IFN and 5-FU in combination does not involve augmentation of the TS inhibition by 5-FU.

Answer 155:

Bibliographic Information

Modulation by recombinant alpha-2a-interfer on the activity and site of action of 5-fluorouracil on xenografted human colon cancer in nude mice: preliminary report. Yoshida K; Fujikawa T; Tanabe A; Sakurai K First Department of Surgery, Jikei University School of Medicine, Tokyo, Japan Nippon Geka Gakkai zasshi (1992), 93(5), 559. Journal code: 0405405. ISSN:0301-4894. Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 1614401 AN 92310370 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Answer 156:

Bibliographic Information

Phase II study: treatment of non-Hodgkin's lymphoma with an oral antitumor derivative of bis(2,6-dioxopiperazine). Ohno R; Yamada K; Hirano M; Shirakawa S; Tanaka M; Oguri T; Kodera Y; Mitomo Y; Ikeda Y; Yokomaku S; + Department of Medicine, Nagoya University School of Medicine, Branch Hospital, Japan Journal of the National Cancer Institute (1992), 84(6), 435-8. Journal code: 7503089. ISSN:0027-8874. (CLINICAL TRIAL); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1538420 AN 92167304 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Although razoxane (ICRF-159), a derivative of bis(2,6-dioxopiperazine), has shown significant antitumor activity in several murine tumors, inadequate bioavailability has limited its clinical efficacy. Sobuzoxane (MST-16), another derivative of bis(2,6-dioxopiperazine), has shown activity against a broad spectrum of murine tumors and human tumor xenografts in nude mice and a lack of cross-resistance to vincristine, doxorubicin, cyclophosphamide, fluorouracil, etoposide, and mitomycin C. These findings suggest that MST-16 has a mode of cytocidal activity different from that of other antitumor agents. PURPOSE: The present late phase II study was conducted to evaluate the clinical efficacy and toxicity of MST-16 in non-Hodgkin's lymphoma (NHL). METHODS: As part of a multi-institutional cooperative study, we conducted a study of MST-16 in 27 patients with NHL who were assessable for drug efficacy and toxicity. MST-16, a bis(2,6-dioxopiperazine) analogue and an inhibitor of topoisomerase II, was administered orally at a dose of 1600 mg/m2 a day for 5-7 days at intervals of 2-3 weeks. RESULTS: Response consisted of one complete remission and seven partial

remissions in 27 assessable patients. Response was achieved at a median of 13 days (range, 9-62 days) after initiation of therapy and lasted a median of 46 days (range, 29-155 days). Major toxic effects were leukopenia in 70% of the patients, thrombocytopenia in 44%, and gastrointestinal disorders in 37%. CONCLUSIONS: MST-16 was shown to be effective in NHL and deserves further clinical trial, since the drug shows little cross-resistance to available antitumor drugs. IMPLICATIONS: Phase II clinical studies of MST-16 in treatment of breast cancer, gastric cancer, and adult T-cell leukemia and lymphoma are also being conducted in Japan. Future trials of combination chemotherapy using MST-16 with other antitumor drugs are warranted in view of the additive effects observed in studies of MOLT-3 cells and studies of L1210 leukemia in mice.

Answer 157:

Bibliographic Information

Enhanced therapeutic efficacy of 5'deoxy-5-fluorouridine in 5-fluorouracil resistant head and neck tumours in relation to 5-fluorouracil metabolising enzymes. Peters G J; Braakhuis B J; de Bruijn E A; Laurensse E J; van Walsum M; Pinedo H M Department of Oncology, Free University Hospital, Amsterdam, The Netherlands British journal of cancer (1989), 59(3), 327-34. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2522792 AN 89194072 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Four human head and neck xenograft (HNX) tumour lines grown in nude mice and two murine colon carcinomas (Colon 26 and 38) were tested for their sensitivity to 5-fluorouracil (5-FU) and its prodrug 5'deoxy-5-fluorouridine (Doxifluridine, 5'd-FUR). 5-FU sensitivity at the maximum tolerated dose (MTD) showed the following pattern; HNX-DU less than HNX-KE = HNX-E = HNX-G less than Colon 26 much less than Colon 38. The sensitivity pattern to 5'd-FUR was: HNX-DU less than HNX-G less than HNX-E less than HNX-KE less than Colon 38 less than Colon 26. For HNX-KE, HNX-E and Colon 26 an increase in therapeutic efficacy was observed with 5'd-FUR as compared to 5-FU; Colon 38 was as sensitive to 5'd-FUR as to 5-FU. Plasma pharmacokinetics of 5'd-FUR and 5-FU were comparable in normal and nude mice. Metabolism of 5-FU and 5'd-FUR was studied in the tumours. Conversion of 5'd-FUR to 5-FU was highest in Colon 26 and 15-20 times lower in HNX-DU, HNX-KE and Colon 38. The Km for 5'd-FUR in all tumours was 1-2 mM. Further anabolism of 5-FU to fluorouridine (FUR) was 5-10 times higher than that of 5-FU to FUR in HNX tumours and 3 times in the colon tumours. 5-FU conversion to FUMP via FUR had the following pattern: Colon 26 much greater than HNX-DU greater than HNX-G greater than HNX-E greater than HNX-KE much greater than Colon 38; of 5-FU to FdUMP via FUdR: Colon 26 greater than HNX-DU = HNX-KE greater than HNX-E greater than HNX-G = Colon 38; and that of 5-FU to FUMP catalysed by orotate phosphoribosyl transferase (OPRT); Colon 26 greater than or equal to Colon 38 greater than HNX-KE greater than HNX-E = HNX-DU = HNX-G. Only those tumours with a relatively high activity of OPRT were sensitive to 5'd-FUR. Colon 26, which has a very high rate of pyrimidine nucleoside phosphorylase, showed a relatively high increase in the therapeutic efficacy. It is concluded that a low rate of pyrimidine nucleoside phosphorylase is enough to convert 5'd-FUR to 5-FU;

further anabolism of 5-FU catalysed by OPRT may be limiting and explain the differential sensitivity.

Answer 158:

Bibliographic Information

The effect of cisplatin and fluorouracil on xenografted human squamous cell carcinoma of the head and neck. Wennerberg J; Biorklund A; Trope C Department of Otorhinolaryngology, University Hospital, Lund, Sweden Archives of otolaryngology--head & neck surgery (1988), 114(2), 162-7. Journal code: 8603209. ISSN:0886-4470. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 3337774 AN 88107064 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

In combined modality treatment, cisplatin and fluorouracil are considered to act synergistically. The assumption is based on results in murine leukemias and has not hitherto been tested on human squamous cell carcinoma. In the present study, cisplatin and fluorouracil, used singly and in combination, were tested on two human squamous cell carcinomas of the head and neck, xenografted to nude mice. Cisplatin (7.5 mg/kg) was given as a single-dose intraperitoneal injection and fluorouracil as repeated intraperitoneal injections every eight hours for four days to a total dose of 200 mg/kg. The toxicity of the cisplatin and fluorouracil combination was lower (27%) than that of fluorouracil alone (50%). Both drugs gave a dose-dependent inhibition of tumor volume growth. Using gained growth delay as endpoint, cisplatin and fluorouracil therapy exhibited a synergistic effect on both tumor lines.

Answer 159:

Bibliographic Information

Subrenal capsule assay for chemosensitivity testing. Kusuyama T; Fujita M; Shimozuma K; Orikasa H; Usugane M; Taguchi T Gan to kagaku ryoho. Cancer & chemotherapy (1987), 14(4), 1143-9. Journal code: 7810034. ISSN:0385-0684. (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 3105468 AN 87183601 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The subrenal capsule (SRC) assay for cancer chemotherapy was tested according to Bogden's methodology. Of 37 patients providing tumor tissue for assay, 29 cases were considered suitable for evaluable assays. Fourteen patients had clinically evaluable diseases and 10 cases were evaluable for SRC assays. Correspondence between sensitive assay and clinical sensitivity was seen in 2 cases, and that between resistant assay and clinical resistance was seen in 4 cases. Discordance between sensitive assay and clinical resistance was seen in 4 cases. In histological studies, cancer tissues implanted in the subrenal space in immunocompetent mice did not show marked proliferation and were replaced by prominent leukocyte infiltration and fibrosis on day 6 after inoculation. The degree of leukocyte infiltration in the xenografts in the mice administered some anti-cancer drugs was slight in comparison with that in untreated control mice, which showed a remarkable trend in xenografts treated with 5-fluorouracil and cyclophosphamide, respectively. Our study suggests that there are many problems involved in the SRC assay methodology of Bogden, and that careful examination of this aspect will be required.

Answer 160:

Bibliographic Information

Sequential combination chemotherapy consisting of vincristine, peplomycin, methotrexate, cis-diamminedichloroplatinum (II), cytosine arabinoside and 5-fluorouracil, for advanced urothelial cancer. Yamauchi T; Hida S; Ooishi K; Okada K; Yoshida O Hinyokika kiyo. Acta urologica Japonica (1985), 31(7), 1093-104. Journal code: 0421145. ISSN:0018-1994. (CASE REPORTS); (ENGLISH ABSTRACT); Journal; Article; (JOURNAL ARTICLE) written in Japanese. PubMed ID 2414981 AN 86047350 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Two VPM-CisCF chemotherapy regimens (vincristine (VCR), peplomycin (PEP), methotrexate (MTX), cis-diamminedichloroplatinum (II) (CDDP), cytosine arabinoside (Ara-C) and 5-fluorouracil (5-FU), established using human bladder cancer xenografts in nude mice were applied for advanced urothelial cancer. VPM-CisCF (I) consisted of 0.4 mg/m2 VCR on days 1 and 4, 2 mg/m2 PEP on days 1-7, 2 mg/m2 MTX on days 2, 3, 5 and 6, 20 mg/m2 CDDP on days 8, 20 mg/m2 Ara-C on days 8 and 13, and 150 mg/m2 5-FU on days 10-12. VPM-CisCF (II) consisted of 0.6 mg/m2 VCR on days 1 and 3, 3 mg/m2 PEP on days 1-4, 3 mg/m2 MTX on days 2 and 3, 35 mg/m2 CDDP on day 4, 20 mg/m2 Ara-C on days 4 and 7, and 200 mg/m2 5-FU on days 5 and 6. These doses were adjusted for each case: the above

mentioned dose x [(80/(40 + Age))2 + (Karnofsky's performance status/100)2]. VPM-CisCF (I) was administered to 6 patients (bladder cancer and transitional cell carcinoma), intra-arterially in two cases. One patient showed a complete response and survived for 7 months, three partial response (PR) surviving for 13, 8 and 37 (arterial-infused case) months, one showed minor response (MR) surviving for 4 months, and one had no change (NC) surviving for 5 months. VPM-CisCF (II) was administered to 11 patients (1 ureteral cancer, 1 renal pelvic cancer, 9 bladder cancer, and 10 transitional cell carcinoma except a case of mixed type of transitional cell carcinoma and squamous cell carcinoma). Four of the patients who had PR survived for 9, 8, 8 and 7 (alive) months, two who had MR survived for 8 and 4 months, three who had NC survived for 6, 4 and 4 months, and who two had progressive disease survived for 8 and 6 months. The major toxicities were myelosuppression and gastrointestinal symptoms, especially nausea and vomiting, but the treatment was well-tolerated.

Answer 161:

Bibliographic Information

The combination of 5-fluorouracil with misonidazole in patients with advanced colorectal cancer. Spooner D; Bugden R D; Peckham M J; Wist E A International journal of radiation oncology, biology, physics (1982), 8(3-4), 387-9. Journal code: 7603616. ISSN:0360-3016. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 7107357 AN 82265071 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Misonidazole (MISO) has produced differential enhancement of tumor cell killing with a range of cytotoxic drugs including 5-fluorouracil (FU) in experimental mouse tumors and human xenografts. Since concomitant enhancement of normal tissue damage has been observed, a Phase I study of MISO and FU has been undertaken in patients with advanced colorectal cancer. Mild nausea and vomiting occurred more frequently after MISO and FU compared with FU alone; however, the incidence of leucopenia was similar with both treatment. No patients receiving the MISO/FU combination developed central nervous system toxicity or peripheral neuropathy. Twenty-four hour plasma nitroimidazole kinetics were analyzed and were not modified by the concomitant administration of the cytotoxic drug. Thus, in this preliminary study FU has been safely combined with MISO without significant modification of plasma nitroimidazole pharmacokinetics. Tumor regression was documented in 2/9 (22%) patients receiving more than 2 courses of MISO/FU. A Phase II study is proposed to investigate tumor response.

Answer 162:

Bibliographic Information

The effect of 5-fluorouracil and adriamycin on heterotransplantation of Noble rat prostatic tumors in congenitally athymic (nude) mice. Drago J R; Maurer R E; Gershwin M E; Eckels D; Palmer J M Cancer (1979), 44(2), 424-30. Journal code: 0374236. ISSN:0008-543X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 476560 AN 80001467 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The Nb rat prostatic adenocarcinoma is a well-characterized, hormonally induced family of tumors that are all readily transplantable into congenitally athymic (nude) mice. Because of this versatile heterotransplantation model, multiple replicate copies of individual tumors can be studied "in rodent." We have extended this by studying the chemotherapeutic response of such tumors and believe that this provides a useful avenue for evaluation of cytotoxic agents. Indeed, this combination of both animal model systems may provide a useful experimental tool to evaluate tumor growth, histopathologic changes and responsiveness to appropriate therapy. We report herein that two Nb rat prostatic

carcinomas (2 Pr-129-D-11A and Pr-90) and thie responsiveness to Adriamycin and 5-fluorouracil are objective by studying both growth rates and tumor histology.